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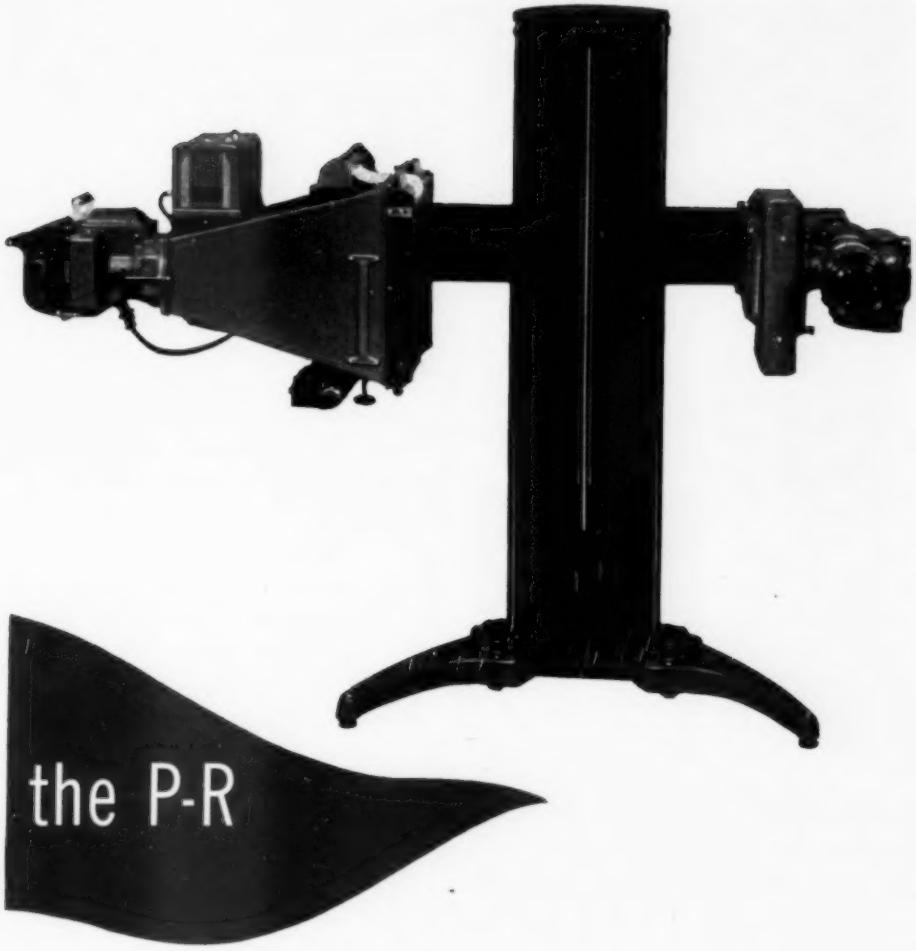

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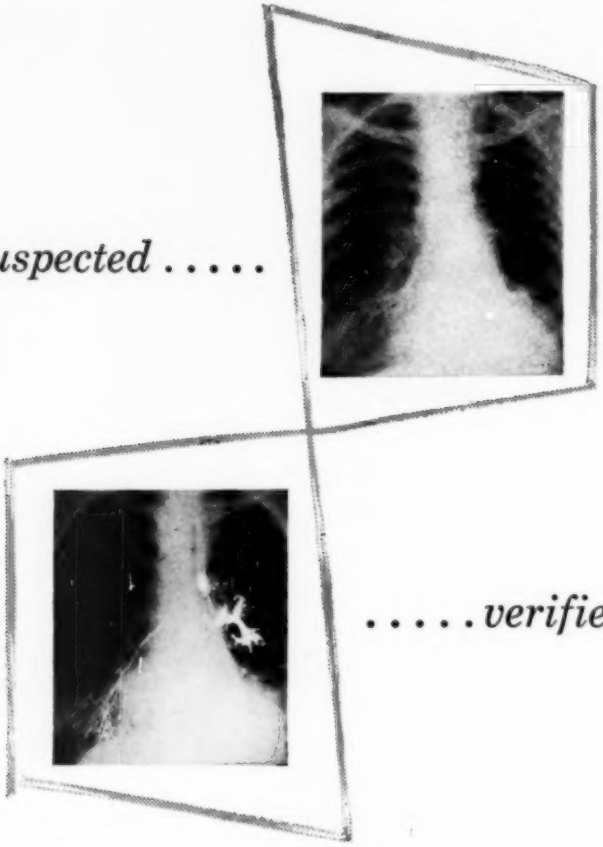

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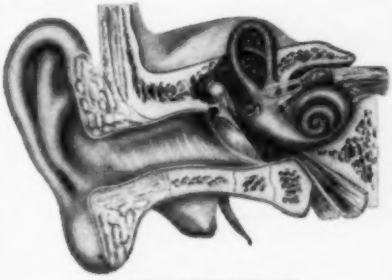

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In Vol. 59, No. 2, 1949, the articles, "Constitutional Factors in Resistance to Infection. I. The Effect of Estrogen and Chorionic Gonadotropin on the Course of Tuberculosis in Highly Inbred Rabbits. II. The Effect of Estrogen on Tuberculin Skin Sensitivity and on the Allergy of the Internal Tissues. III. On the Mode of Action of Estrogen and Gonadotropin on the Progress of Tuberculosis", the following correction is to be made:

In paper I, omit the footnote "per cubic centimeter of free flowing, venous blood" from tables 1, 2, 3 and 4.

In paper II, omit the footnote "per cubic centimer of free flowing, venous blood from tables 2 and 3.

INCIPIENT PULMONARY TUBERCULOSIS IN PERSONS OVER FORTY[1]

AARON D. CHAVES

(Received for publication December 24, 1948)

INTRODUCTION

There is a rather widespread clinical impression that pulmonary tuberculosis rarely makes its appearance after the age of thirty. For example, in the most recent edition of an outstanding textbook of medicine (1) the following statement is found in the section on tuberculosis: "Those who have lived to the fourth decade without the appearance of a plumonary lesion seldom develop the disease." Nevertheless, it is the impression of many phthisiologists (2, 3, 4) that the first roentgenographic evidence of significant pulmonary tuberculosis after thirty, and even after forty, is not at all a rarity today. For instance, of the 344 cases of incipient pulmonary tuberculosis recently reported by Reisner (2), 17 developed after the age of forty. It was thought worthwhile, therefore, to report an additional 5 cases of incipient pulmonary tuberculosis in persons over forty years recently observed by the author.

Source of Material and Selection of Cases

The 5 cases reported here were observed by the author since his assignment in April, 1946 to the Kips Bay Health Center Chest Clinic, one of the twenty-one chest clinics of the Bureau of Tuberculosis, Health Department, New York City. This clinic averages approximately 2,000 adult "contact" examinations yearly. The established policy is to follow all adult contacts to active cases of pulmonary tuberculosis every six months with complete chest examination, including a roentgenogram, as long as contact is maintained and for two years after contact has been broken. With only few exceptions, the population served by the clinic is white and the overwhelming majority of the contacts supervised (the exact per cent is difficult to determine) are below forty years of age.

All 5 patients included in this study, which ended September, 1948, had recent "normal" chest films as "contacts" which were carefully reviewed by the author and all developed the first roentgenographic evidence of tuberculosis after their fortieth birthday. Except for age, the same criteria for inclusion in this group of cases were used as is described by Reisner in his articles (2).

CASE REPORTS

Case 1: L. P. (figures 1A and 1B) is a white male born in 1899. He was a contact to his wife who had apparently arrested far advanced pulmonary tuberculosis at the time of his first examination at the Kips Bay Clinic on April 16, 1942. This film was entirely "normal" (figure 1A). On the next clinic visit, February 21, 1945 (at which time patient was 46 years

[1] From the Bureau of Tuberculosis, New York City Department of Health, 125 Worth Street, New York 13, New York, and the Departments of Medicine and Preventive Medicine of the New York Hospital-Cornell University Medical College.

TABLE 1

Observations at the Time of Initial Demonstration of the Pulmonary Lesion

(5 cases personally observed combined with 17 cases from Doctor Reisner's series to make a total of 22)

MONTHS FROM LAST NORMAL CHEST ROENTGENOGRAM TO INITIAL LESION	TOTAL NUMBER	STAGE OF DISEASE AT FIRST APPEARANCE[1]			SYMPTOMS	
		Minimal	Moderately Advanced	Far Advanced	Present	Absent
4 to 6	9	7	2		3	6
7 to 12	10	6	2	2	3	7
13 to 24	1		1		1	
Over 24	2		1	1	2	
Total	22	13	6	3	9	13

[1] According to criteria of National Tuberculosis Association.

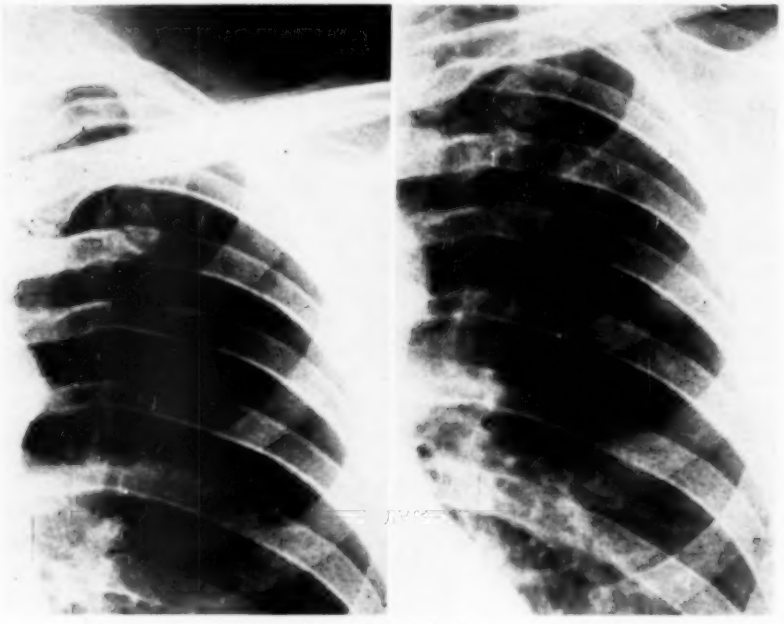

FIG. 1 (Case 1, L. P.)

A. (Left) April 16, 1942, normal chest (detail of left upper lung field).

B. (Right) March 24, 1948, area of infiltration in first a.i.c.s. on left. This lesion had been unstable between February 21 and May 29, 1945. No interval films available. Now considered arrested.

old) he complained of cough with the expectoration of blood-streaked sputum during the preceding two weeks. A chest roentgenogram, obtained at that time revealed definite infiltration in the left upper lung and the diagnosis of active, moderately advanced pulmo-

nary tuberculosis was made. The patient never placed himself under adequate treatment and very few sputum examinations were done (all negative for *M. tuberculosis*). Subsequent chest films on March 9, 1945 and May 29, 1945 revealed progression of infiltrations and probable cavitation in the left upper lung. The patient was lost from supervision until March

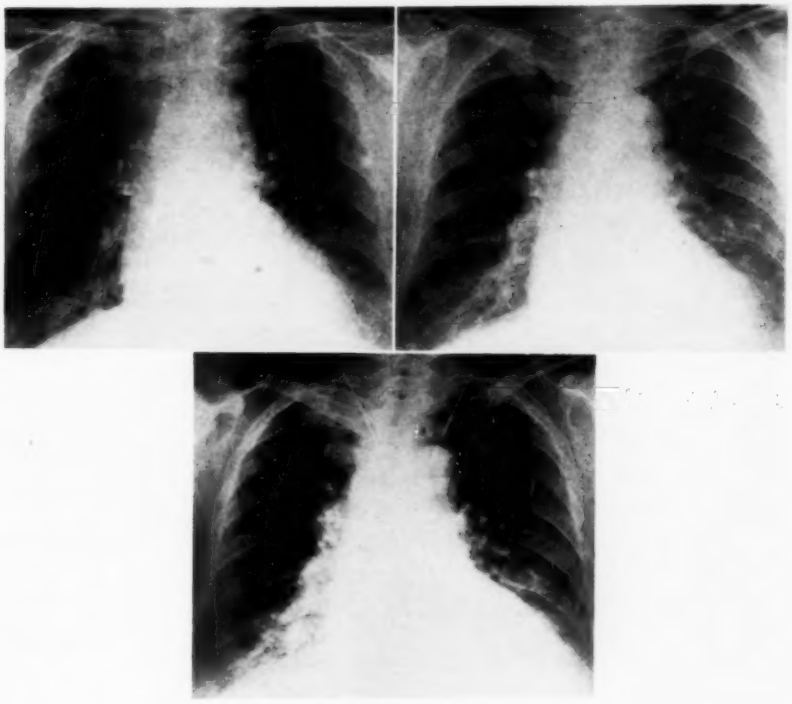

FIG. 2 (Case 2, M. W.)

A. (Upper left) January 23, 1946, cardiac enlargement and wide aorta (hypertensive) Lung fields considered normal. Calcification at right hilum.

B. (Upper right) January 31, 1947, round area of infiltration, periphery of first a.i.c.s. on right. In previous film of July 29, 1946, there was a larger area of infiltration which decreased considerably in size in the six month interval.

C. (Bottom) March 15, 1948, extension and breakdown of lesion in right upper lung field, between first and third anterior ribs. There is probably a small lesion below first rib on the left.

24, 1948, when a chest film (figure 1B) revealed clearing and "hardening" of the lesions, and he stated that he was entirely asymptomatic. The diagnosis was changed to arrested moderately advanced pulmonary tuberculosis. The total period of observation from first recognition of disease was three years.

Case 2: M. W. (figures 2A to 2C) is a white female born in 1886, with known hypertensive cardiovascular disease and mild diabetes, whose daughter died of pulmonary tuberculosis in August, 1947. The first chest roentgenogram at Kips Bay Clinic was taken on January

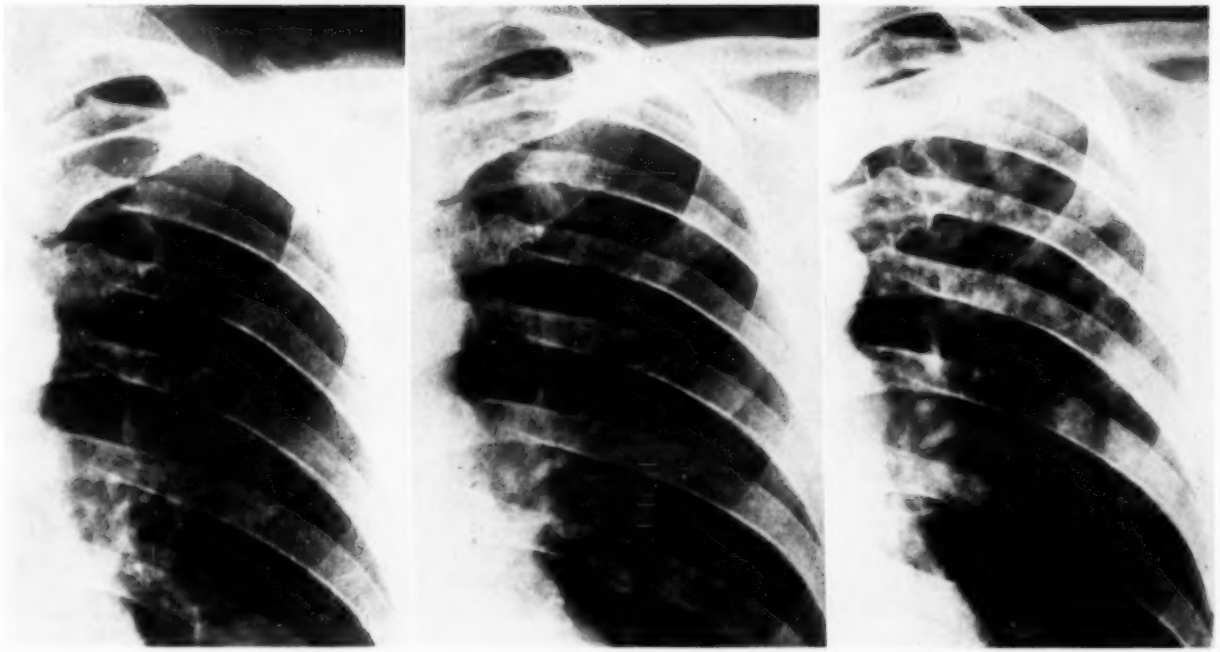

FIG. 3 (Case 3, J. P.)

A. (Left) May 4, 1945, normal chest (detail of left upper lung field).
B. (Center) December 13, 1946, soft infiltrations in first interspace, left lung.
C. (Right) January 17, 1947, marked progression, left lung.

23, 1946 and revealed an enlarged heart, a widened aorta and only a calcified primary complex in the lung (figure 2A). The next routine film of July 29, 1946 (when patient was 60 years old) revealed a round homogeneous density, 2 cm. in diameter, in the first intercostal space on the right. The density subsequently first decreased in size (figure 2B) and then showed definite progression (figure 2C). Sputum examinations from November, 1946 until September, 1948 were consistently positive for acid-fast bacilli on direct examination. The patient was admitted to Triboro Hospital in September, 1948 with moderately advanced cavitary disease. She always denied having symptoms and was extremely reluctant to accept hospitalization. The total period of observation was approximately two years, during which time the pulmonary tuberculosis progressed from a minimal to a moderately advanced state.

Case 3: J. P. (figures 3A to 3C) was a white male born in 1903 who had been heavily exposed to a friend who died of pulmonary tuberculosis in 1945. Roentgenograms obtained at the clinic between May 4, 1945 (figure 3A) and May 22, 1946 were all interpreted as normal. Routine films on November 27, 1946 and December 13, 1946 (when patient was 43 years old) revealed a very small soft infiltration in the first anterior intercostal space on the left (figure 3B). Patient was immediately recalled for sanatorium care, but did not report to the clinic until January 17, 1947, at which time his chest film revealed marked progression of the disease involving the upper half of the left lung field (figure 3C). He was promptly admitted to the New York Hospital, where his sputum was found to be positive for *M. tuberculosis*. He was given a course of streptomycin and transferred to a sanatorium after considerable improvement and disappearance of *M. tuberculosis* from the sputum. He soon had a reactivation of the disease in his left upper lobe, however, and the sputum again contained *M. tuberculosis*. The reactivated lesions did not respond to bed rest and a second course of streptomycin. An attempt at left pneumothorax was unsuccessful, so a first stage thoracoplasty was done in April, 1948. He died shortly after the operation. Postmortem examination revealed that an acute myocardial infarction was the cause of death. The total period of observation from discovery of minimal lesion to death was approximately sixteen months.

Case 4: S. D. (figures 4A to 4D) is a white female, born in 1890, who had had mild diabetes for many years and contact with an open case of pulmonary tuberculosis (husband) since March, 1942. She was examined regularly at the clinic, with normal chest roentgenograms between October 18, 1943 and May 20, 1946 (figure 4A). Films of May 20, 1946 and December 9, 1946 (when patient was 56 years old) revealed a very small soft infiltration which was overlooked as it was covered by the posterior part of the fifth rib on right. A routine film of the chest on January 12,1948 and re-examination on January 21, 1948 revealed a homogeneous exudative infiltration in the right upper lung (figure 4B). The patient was asymptomatic and refused hospitalization. Subsequent films in the clinic revealed marked progression of the disease with formation of a large cavity in right upper lung (figures 4C and 4D). Sputum concentrations and cultures were reported negative for *M. tuberculosis* until April 19, 1948. Since then, all sputum examinations have been positive for *M. tuberculosis*. The patient still denies symptoms and refuses hospitalization. Her diabetes is fairly well controlled by a regimen supervised by a diabetic clinic. The total period of observation from first appearance of the minimal lesion to the present far advanced bilateral pulmonary tuberculosis is nineteen months.

Case 5: T. M. (figures 5A and 5B) a white male born in 1895, was admitted to the clinic on August 22, 1947 as a contact to a friend who died in August, 1947 of tuberculosis. The first roentgenogram of the chest on August 22, 1947 was interpreted as normal (figure 5A). A routine film of February 20, 1948 (when patient was 53 years old) revealed a soft infiltration in the third anterior interspace on the right which had already showed considerable progression by March 3, 1948 (figure 5B). The patient was promptly hospitalized at Bellevue Hospital, where *M. tuberculosis* was found in the sputum, He was subsequently transferred to the Municipal Sanatorium at Otisville, where he has remained up to the present (September, 1948). The sputum is still positive for *M. tuberculosis*. The total period of observa-

tion from the initial demonstration of a minimal lesion to the present status, as active moderately advanced tuberculosis with tubercle bacilli in the sputum, is five months.

FIG. 4 (Case 4, S. D.)

A. (Upper left) April 24, 1944, normal chest.

B. (Upper right) January 21, 1948, soft infiltration, periphery of right lung, between first and second a.i.e.s.

C. (Lower left) April 19, 1948, marked progression on right. New lesion on left (behind intersection of third and sixth ribs).

D. (Lower right) July 14, 1948, further progression bilaterally, with cavity formation on right.

Analysis of Combined Series

It was thought worth while to combine these 5 cases with the 17 cases of pulmonary tuberculosis developing after forty years of age included in Reisner's large series of incipient pulmonary tuberculosis. This makes a group of 22 cases ob-

served in various New York City Health Department Clinics, for the most part, since 1940. One cannot expect to learn too much from analyzing such a small group of cases derived from material with the many shortcomings already discussed in Reisner's recent articles (2). Nevertheless there are in this group notable clinical features.

The ages varied from 40 to 75; 9 were male, 15 female; 17 were white and 5 nonwhite. All of the patients were known to have had recent intimate contact with active cases of tuberculosis. Five patients presented roentgenographic

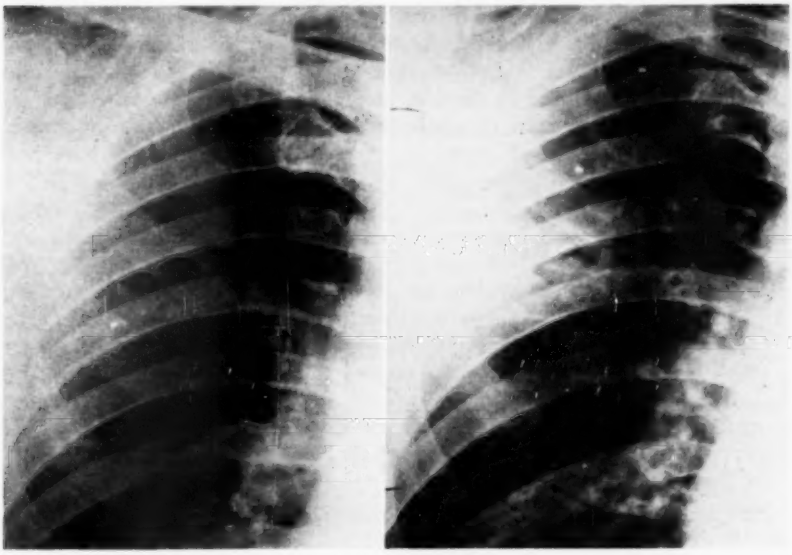

FIG. 5. (Case 5, T. M.)

A. (Left) August 22, 1947, normal film (detail of right upper lung field).

B. (Right) March 3, 1948, soft patchy infiltration in periphery of right lung between third and fourth a.i.c.s.

evidence of a healed, calcified, primary complex. No tuberculin testing was done on any of the patients prior to development of recognizable tuberculosis. In all but 5 instances, bacteriologic confirmation of the diagnosis was obtained at some time during the period of observation. The sputum investigations made early in the disease in most instances were not sufficiently intensive to be of much significance.

Observations at the time of initial demonstration of the pulmonary lesion: In table 1 are listed some of the observations made at the time of initial appearance of the pulmonary lesion. Nineteen cases were observed to develop disease within one year of a normal roentgenogram, while 3 (all with symptoms) were first discovered with disease approximately two, three and four and one-half years

respectively after a normal film. The latter were already advanced cases on discovery. While it is obvious that the earlier the lesion is discovered, the greater the chance of its being minimal, asymptomatic, and noninfectious, it is interesting to find that 2 nonwhite patients with moderately advanced disease with sputum positive for *M. tuberculosis* were encountered only six months after a normal film. One 45 year old white woman developed far advanced disease (fatal within one and one-half months after diagnosis) seven months after a normal film. Four of the 13 minimal cases were found to have *M. tuberculosis* in the sputum at the time of discovery.

As is to be expected, there were many cases in this group associated with other diseases. Four patients had mild, uncontrolled diabetes at the time of discovery, one of the diabetics also having hypertension and one arteriosclerotic heart disease. In his paper on early pulmonary infiltration, Amberson (5) mentions diabetes as one of the factors which predispose to the late development of progressive

TABLE 2

Observations at Conclusion of Period of Observation (September, 1948)

STAGE OF DISEASE AT INITIAL DEMONSTRATION	STATUS AT CONCLUSION OF OBSERVATION			
	Arrested	Active		Dead
		Minimal	Moderately or far advanced	
Minimal (13 cases)	4	2	4	3
Moderately advanced (6 cases)	4*			2
Far advanced (3 cases)				3
Total	8	2	4	8

* 2 cases with disease controlled with pneumothorax.

tuberculosis. However, none of the patients, as far as could be ascertained, had "dietary deficiencies, alcoholism and the like", also listed by Amberson as factors usually associated with late development of pulmonary tuberculosis. Three patients had hypertension with cardiac enlargement (one diabetic) and 2 had arteriosclerotic heart disease (one diabetic). One patient died of a myocardial infarction following a first stage thoracoplasty (J. P., Case 3). One patient had latent syphilis and one presented temporary manifestations of a psychosis.

Observations at conclusion of period of observation: The status of the 22 cases at the conclusion of the period of observation, which varied from six months to ten years and averaged 39 months, will be found in table 2. The striking finding in this small series is the extreme seriousness of the disease. Eight of the 22 patients have already died, and 4 patients are considered at present to have progressive and advanced tuberculosis with a rather poor prognosis. Only 8 cases are classified as arrested, 2 with the aid of pneumothorax. In the 8 fatal cases, duration from initial discovery to death varied from one and one-half months in a case which was far advanced to six and one-half years in a case which was mini-

mal at time of discovery. Two of the patients with minimal lesions died sixteen and seventeen months, respectively, after initial demonstration of the lesion, one from myocardial infarction and the other from rapidly progressive tuberculosis complicated by diabetes. Of the 4 diabetics, the tuberculosis of one is now well arrested, one is dead, and 2 have progressive and advanced tuberculosis with a poor prognosis. The type of treatment administered to the 22 patients varied considerably from prompt, excellent care, to no treatment at all.

COMMENT

One outstanding fact is evident from the study: a roentgenographically normal chest in a person over 40 does not eliminate the possibility of pulmonary tuberculosis developing in the future. As a matter of fact, incipient pulmonary tuberculosis in persons over 40 may be much more common than is generally supposed. From discussions with many observers, it is the author's impression that more and more cases of early tuberculosis in the older age group are being seen in various chest clinics throughout the country. Reisner (2) and Robins (4) have both called attention to the late appearance of the initial roentgenographic evidence of pulmonary tuberculosis in many cases under their observation, while both Pinner (3) and Reisner (2) have recently indicated the need for serial roentgenographic observations in the older age groups among the apparently healthy population to determine the frequency of incipient clinical tuberculosis in such groups.

It is impossible, of course, to draw any conclusions as to the pathogenesis of incipient clinical pulmonary tuberculosis in older people from this very small series of cases drawn from a highly selective sample of the population. Theoretically, late incipient pulmonary tuberculosis may come about as the result of: (*1*) reactivation of old roentgenographically undetectable foci (endogenous exacerbation); (*2*) new exogenous infection in individuals with a clinically healed primary complex as determined by a positive tuberculin test; (*3*) new exogenous infection in individuals with an obsolete primary infection which can be determined clinically by the reconversion of a previously known positive tuberculin test to negative (second "primary infection"); (*4*) recently acquired first infection (true primary infection).

The entire problem of pathogenesis might be clarified to some extent by determining the frequency with which incipient tuberculosis occurs in older individuals who are negative tuberculin reactors shortly prior to the initial demonstration of pulmonary tuberculosis. Unfortunately, there are no up to date data on the incidence of negative tuberculin reactors in the older age groups, and the need for such a study becomes obvious. Both Pinner (3, 6) and Rich (7) have indicated the need for large periodic tuberculin surveys of apparently healthy populations of all ages, *including those over 40 years of age.*

The importance of clear understanding of the pathogenetic mechanisms of pulmonary tuberculosis in the older age groups can be readily understood in view of the marked change in the epidemiological picture of the disease, with a striking shift of the mortality peak towards the older age groups. While

in 1900 only about 25 per cent of all tuberculosis deaths occurred after the age of 45 (3), at present 50 per cent of all tuberculosis deaths in this country occur after the age of 45 (8). If one considers the white males alone, over 75 per cent of tuberculosis deaths today (in New York City) occur after the age of 40 (9). Proper public health methods for the control of tuberculosis may well depend to a considerable extent on a better understanding of all the factors contributing to this remarkable shift in the peak mortality.

On the basis of the findings of this small and highly selective series, one gets the impression that, in the material available from a "contact" population, the incipient tuberculous lesions of persons over 40 show about the same tendency to progression as those under 40. The applicability of these observations to incipient lesions found among the general population remains to be determined.

SUMMARY

1. Five cases of incipient pulmonary tuberculosis in persons over 40 years of age are reported. All 5 patients had a recent normal chest roentgenogram.

2. Of this group of 5 cases, one died of a myocardial infarction following a first stage thoracoplasty, 2 have active progressive disease complicated by diabetes, one has active, moderately advanced tuberculosis, and the infection in one is arrested.

3. By adding these 5 cases to 17 cases of incipient pulmonary tuberculosis in persons over 40 observed by Reisner, a total of 22 cases are made available for study. Of this group, 8 are dead, 4 have active and progressive disease with a poor prognosis, 2 have active but minimal lesions, and the disease in 8 was considered to have been arrested at the conclusion of the period of observation.

4. The need for serial roentgenographic observations and repeated tuberculin surveys in the older age groups is discussed.

SUMARIO

Tuberculosis Pulmonar Incipiente en los Cuarentones

1. Comunícanse cinco casos de tuberculosis pulmonar incipiente en personas de más de cuarenta años. Los 5 enfermos habían mostrado recientemente una radiografía normal.

2. De los 5, uno ha muerto de infarto miocardíaco consecutivo al primer tiempo de una toracoplastia, 2 tienen tuberculosis evolutiva activa complicada con diabetes, uno tiene tuberculosis moderadamente avanzada, activa, y en uno la infección está estacionada.

3. Agregando estos 5 casos a los 17 de tuberculosis pulmonar incipiente observados por Reisner en personas de más de 40 años, cuéntase para estudio con un total de 22 casos. De este grupo, 8 han muerto, 4 tienen tuberculosis evolutiva y activa con mal pronóstico, 2 tienen lesiones activas, pero mínimas, y 8 parecían hallarse estacionados al terminar el período de observación.

4. Discútese la necesidad de ejecutar observaciones radiográficas seriadas y repetidas encuestas con tuberculina en los grupos de mayor edad.

Addendum

Since submitting this paper for publication four months ago, the writer has observed 9 additional cases of incipient pulmonary tuberculosis in persons over 40 years of age which fulfill the criteria for inclusion in this study. Two of the cases were seen at the Kips Bay Chest Clinic; 3 cases were observed on the Chest Service of the New York Hospital; one was seen on the Pulmonary Service of Montefiore Hospital; 3 cases were reviewed (charts and roentgenograms) from other New York City Health Department Chest Clinics.

Five patients were male, 4 were female; 6 were white and 3 were Negro. The interval between the last normal chest film and the initial roentgenographic evidence of disease varied from six months to ten years, with most intervals between six and twelve months. Ages of the patients at the time of the last normal chest films ranged from 40 to 62 years.

Six patients had definite symptoms antedating the discovery of disease, 2 of whom had significant exposure recently to tubercle bacilli. All 6 of these patients had far advanced active pulmonary tuberculosis with sputum positive for *M. tuberculosis* at the time of discovery. Three cases were discovered as the result of a routine interval chest film taken during the course of supervision of a "contact." These 3 individuals had lesions of minimal extent and were asymptomatic at the time of discovery.

During January, 1949 the Bureau of Tuberculosis of the Department of Health, New York City, conducted its *second* survey of the Municipal Lodging House, a city institution which offers shelter to homeless and destitute men. Two thousand five hundred and seventeen photofluororoentgenograms were taken of men who, for the most part were over 40 years of age, with the average age 56 years. Many of those examined had been included in the first Municipal Lodging House survey conducted in 1940–1941. Fortunately, the films of the original survey eight years ago were preserved on microfilm.

A detailed report of the findings of this recent survey will be published in a forthcoming paper. However, there are already available data which, although incomplete, are of sufficient interest to warrant inclusion here. Nineteen men, with normal survey films in 1940–1941 (as determined by reviewing the microfilms of the original survey roentgenograms) had roentgenographic evidence in their recent examinations highly suggestive of clinically significant pulmonary tuberculosis. *Sixteen of these cases were over 40 years of age at the time of the normal survey film, eight years ago.*

The detailed examination of these cases is still incomplete, although all of the patients have had 14 by 17 films taken. Sputum studies on most of the cases, however, are not as yet available. On the basis of the roentgenograms alone, therefore, the following preliminary diagnoses were made in these 16 cases:

Active far advanced pulmonary tuberculosis in 3 cases.

Active moderately advanced pulmonary tuberculosis in one case.

Minimal to moderately advanced pulmonary tuberculosis of undetermined activity in 11 cases.

Arrested minimal pulmonary tuberculosis in one case.

Acknowledgment

The author is deeply grateful to Dr. David Reisner, Denver, Colorado, for giving him permission to review his personal records on the 17 cases included in his study on incipient pulmonary tuberculosis.

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TUBERCULOSIS IN THE GERMAN POPULATION, UNITED STATES ZONE OF GERMANY[1]

PHILIP E. SARTWELL,[2] CHARLES H. MOSELEY[3] AND ESMOND R. LONG[4]

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INTRODUCTION

The rise in tuberculosis mortality which accompanied World War I in all the belligerent countries of Europe gave promise of a similar rise after the last war, with its even greater devastation and longer duration. Such a rise did occur and was proportionately though not absolutely greater than that in World War I.

During the past year a number of reports have appeared dealing with the current tuberculosis situation in Germany. From certain of these reports, and from other sources, an impression has been formed not only that there has been a disastrous increase in the disease but that it is continuing to increase. Such opinions are to a large extent based upon the increase in reported tuberculosis morbidity. Other studies, which have placed more emphasis on mortality data, have come to different conclusions.

A survey of the postwar situation in the United States Zone of Germany, conducted by the authors in February, 1948 as members of a Commission of the Department of the Army, had as one of its objectives the collection of information on the extent of the rise in tuberculosis and the immediate postwar trend in that area. In view of the conflicting opinions mentioned above, it is believed worth while to present the evidence which was obtained. The data will be discussed under two main headings: first, mortality, with consideration of changes by age, sex, and form of disease; and second, morbidity, with discussion of factors responsible for apparent changes in morbidity rates. Brief consideration will also be given to the present program for tuberculosis control.

Mortality

In analyzing the present problem, it is pertinent to consider the rise in mortality which accompanied World War I. This has been reviewed by Drolet (8) who gives data showing that of 24 countries, mostly in Europe, all but 5 had a wartime rise. In 3 of these countries the highest rate was reached in 1916; in 3 it came in 1917, and in 13 it came in 1918. The influenza epidemic of that year

[1] This paper is based upon the findings of a Commission appointed by the Secretary of the Department of the Army and organized by Mr. Tracy S. Voorhees, Assistant to the Secretary, and Col. Tom F. Whayne, MC, Chief of the Preventive Medicine Division, Office of The Surgeon General. The members of the Commission were Doctor Long, Doctor Sartwell, Col. Silas B. Hays, and Maj. Alonzo W. Clark. In Germany the group was joined by Lt. Col. Moseley.

[2] Assistant Professor of Epidemiology, The Johns Hopkins School of Hygiene and Public Health, Baltimore, Maryland.

[3] Lt. Colonel, MC, U. S. Army, Military Government, Land Hesse, Germany.

[4] Director, The Henry Phipps Institute, Philadelphia, Pennsylvania.

undoubtedly caused the 1918 rates to be higher than they would otherwise have been. In none of the 24 countries was there a postwar rise between 1918 and 1920, although in several the 1920 rate remained higher than that for 1913. The promptness with which tuberculosis mortality responded to war and postwar changes is remarkable. How much of the rise resulted from the deaths of persons already suffering from active tuberculosis and how much from new infections or reactivation of old disease cannot be determined.

In Germany the mortality rate, which had been declining for a number of years, began to rise in 1915, was highest in 1918, and then fell off sharply to a point in 1920 which was just above the prewar level. With the disastrous inflation and depression of 1922–1923 a second but less marked rise occurred, succeeded by a further steady decline up to the beginning of World War II. In 1939 only four countries, Denmark, Australia, the Netherlands and the United States, had mortality rates lower than Germany's rate of 50 per 100,000.

Rather promptly at the beginning of World War II tuberculosis mortality began to rise in most of the belligerent European countries (2, 3, 6). The worst situations developed in Poland, Yugoslavia, Greece and Austria. On the other hand, Switzerland, Sweden and Denmark, countries which were not directly involved in the fighting, escaped any appreciable rise. The peak year of mortality was 1941 in the cities of London, Brussels and Paris; 1942 in Prague; 1944 in Rome and Warsaw; and 1945 in Amsterdam and Vienna. Daniels states that "the number of additional deaths from tuberculosis during the war must run into many hundreds of thousands, and the number of surviving sufferers must number between 5 and 10 million." It is, however, encouraging to note that in nearly all the war-torn countries tuberculosis as measured by mortality is again on the decline, and that in a considerable number of these countries it is already below the prewar level (6).

At the time of an official visit by one of the authors to Germany in October, 1945 (10), several adverse factors were noted which created a most grave situation. These included: a shortage of beds (less than one bed for tuberculosis per annual death), and a large number of open cases living at home; a housing shortage (density of population 1.5 to 2.5 persons per room in the large cities); nutritional difficulties; and the fact that before the close of hostilities patients with open tuberculosis had been generally permitted to work in factories and other industrial plants. This last factor was thought to have led to a spread of the disease which would become evident with the passage of time. A second visit in August, 1947 (11) revealed marked improvement in the bed situation and other tuberculosis control measures and permitted a more optimistic view.

The difficulties in the way of obtaining accurate mortality data from Germany for the war and postwar periods are great. In the first place, there have been mass migrations since the war which have made it very difficult to estimate populations. Large numbers of German prisoners of war (Wehrmacht) have been repatriated; there has been a great influx of displaced persons; and there has been a large immigration of German national expellees from Czechoslovakia and Poland. These immigrations have produced a considerable net increase

in the population of the U. S. Zone. The increase from 1939 to October, 1946, when a census was taken, was about 2.5 million, or about 18 per cent of the 1939 population, and was due chiefly to postwar immigration rather than to natural increase (12). There was a large excess of females, especially in the age span 20 to 29, between which ages in October, 1946 the ratio was 17 females to every 10 males.

Data on tuberculosis mortality are also subject to several errors. While official death registration figures have been used almost entirely, it should be noted that in some areas death certificates have until recently been signed by laymen. The changes in boundaries of the Länder or provinces within the U. S. Zone have rendered comparison of current mortality with earlier data impossible except in the case of Bavaria, which has remained largely unchanged in territory. Members of the German military forces are understood to be excluded from both population and mortality statistics from 1939 to the end of the war. The inclusion

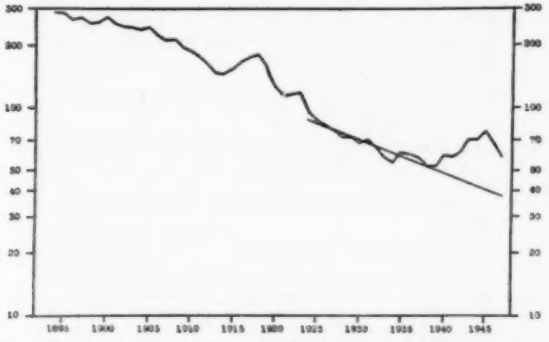

FIG. 1. Mortality rates for pulmonary tuberculosis, Bavaria, by year, 1894–1947

of displaced persons in mortality statistics is uncertain during a part of the postwar period. Finally it must be remembered that the disruption of German civil organization in the latter part of the war and immediate postwar period has undoubtedly reduced the accuracy of all statistics for this period; in fact, for some places such data are wholly lacking.

In spite of these deficiencies, it is fairly clear that tuberculosis mortality began to rise in most parts of western Germany in 1939 or 1940 and continued upward until about 1945. Since then it has been on the decline. The extent of the rise in western Germany was rather small by comparison with other parts of southeastern and central Europe. In Berlin, however, where the prewar rate was somewhat higher than elsewhere in Germany, the wartime rise was very large.

The statistics for Bavaria, which have been recently published (13, 15) will be examined in detail. Bavaria is a largely agricultural state in the south of Germany, its principal city being Munich. Little change was made in its territorial limits after the war. In figure 1 may be seen the trend of pulmonary tuberculosis mortality in Bavaria from 1894 to 1947, the scale of rates being logarithmic.

The trend line drawn on this graph is fitted by the least squares method employing the logarithms of the rates from 1924 to 1938. It is seen that both wars produced very similar interruptions in the long time downward trend of mortality, the rise in World War II being proportionately greater owing to the longer duration of hostilities and the other factors already mentioned. It is also apparent that the postwar decline has thus far been like that following World War I.

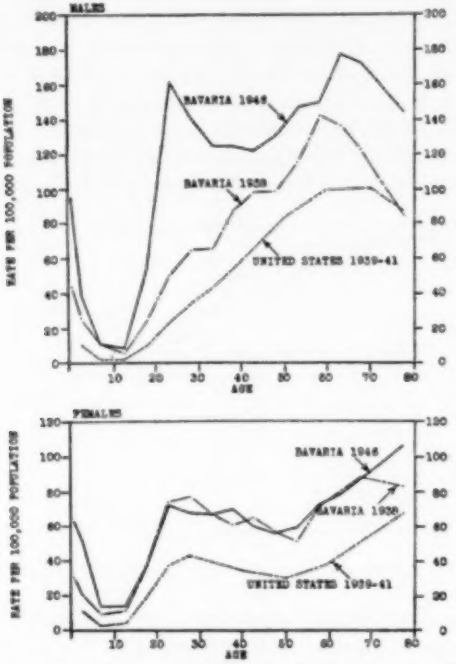

FIG. 2. Mortality rates for all forms of tuberculosis by sex and age, Bavaria and United States.

An attempt was made to obtain age- and sex-specific mortality rates for Bavaria, in order to show what population group was chiefly responsible for the excess mortality. The difficulty was not so much in the enumeration of deaths as in relating them to the population by age groups. It is emphasized that, owing to the extensive migrations mentioned above, the accuracy of these rates is open to question. They are presented in figure 2, however, as giving some indication of where the excess lies. In this graph (figure 2), age-specific rates for each sex are shown for the years 1938 and 1946, with the corresponding rates for the white population of the United States averaged for 1939–1941 (the age groups being slightly different).

In 1938, Bavaria's age distribution of mortality in both sexes was roughly

parallel to, although somewhat higher than, that in the United States. In 1946 the mortality for males was greatly increased in infancy and in all adult age groups. The most marked excess was in the 20 to 34 year age span. The opinion was expressed by German health officers that excessive mortality among repatriated prisoners has contributed to this high rate. Roentgen surveys of such groups have revealed a high prevalence of significant tuberculosis.

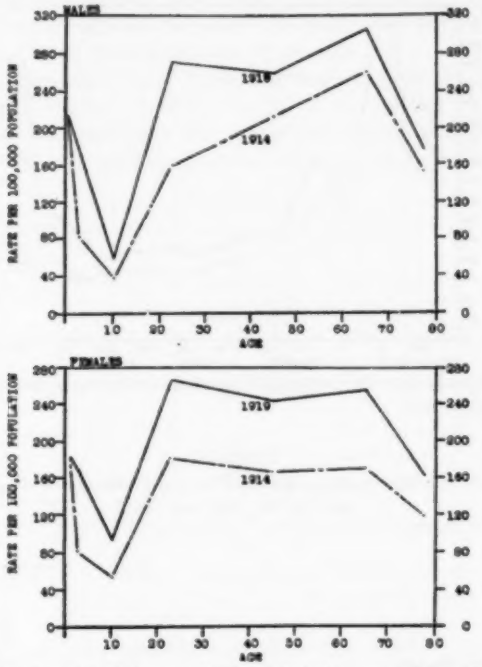

FIG. 3. Mortality rates for all forms of tuberculosis by sex and age, Germany, 1914 and 1919.

Among females, on the other hand, the only population groups showing an increase in 1946 as compared with 1938 were infants and young children, among whom a rise similar to the male rise was recorded. There was practically no difference between prewar and postwar mortality in adult females. Presumably had there been no war, the 1946 rates would have shown a decrease, but at least there was no rise. The increase in infant mortality from tuberculosis in both sexes suggests that, in this age group at least, the frequency of infection was greater in 1946 than before the war.

For comparative purposes, death rates for all Germany for the years 1914 and 1919 were obtained (14) and are shown in figure 3. It will be noted that in World War I the increase in male mortality was much the same as in World

War II; but female mortality also increased at all ages in about the same way as male mortality, in contrast to what happened in Bavaria in World War II.

The other Länder in the U. S. Zone have experienced rises and declines in tuberculosis mortality quite similar to that of Bavaria. The evidence indicates that mortality was highest in 1945 and has steadily fallen since that year. Indications of this are seen in figure 4 in which the trend of tuberculosis mortality

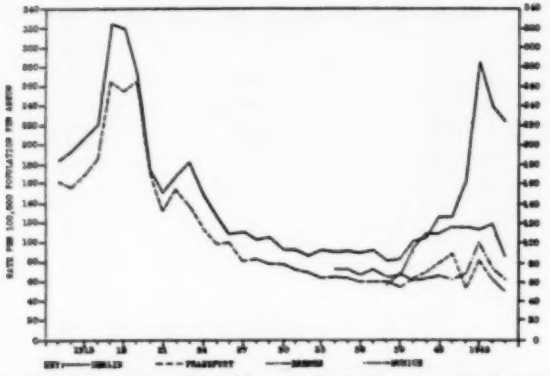

FIG. 4. Tuberculosis mortality, selected large cities in Germany, death rates for all forms of tuberculosis, 1913–1947.

TABLE 1

*Mortality Rates per 100,000 Population for all Forms of Tuberculosis, U. S. Zone of Germany and Berlin, 1946 and 1947**

	MORTALITY RATE	
	1946	1947
Land Bavaria	75	67
Land Hesse	72	69
Land Württemberg-Baden	77	67
Bremen (city only)	119	87
Berlin (entire city)	239	223

* See text for comments on reliability of rates.

rates for four German cities, all of them except Berlin being in the U. S. Zone, are depicted, and in table 1, which gives rates for 1946 and 1947 in each part of the U. S. Zone.

Land Hesse shows an excess in mortality of adult males from age 20 upward. This excess is noted both by comparison with female rates and with prewar male rates. Thus, despite the considerably larger number of females in the population, there were 1,733 male deaths from tuberculosis in 1947 and only 1,136 female deaths. Among males, tuberculosis accounted for 7 per cent of all deaths; among females, for 5 per cent. In Frankfort, the largest city of Land Hesse, the

data furnished indicated that the tuberculosis mortality rate by 1947 had already fallen below the prewar level despite the fact that Frankfort suffered heavily by bombing and the resultant overcrowding. Frankfort's increase in mortality was mostly limited to adult males and especially males over the age of 50, there being little change in female rates between 1938 and 1946.

Land Württemberg-Baden in 1947 reported 1,443 male deaths and 1,046 female deaths from tuberculosis, the excess among males being chiefly from age 30 upwards. Among males 6.8 per cent of all deaths were from tuberculosis while the corresponding figure for females was 5.2 per cent.

The territory comprising Land Bremen, a small area on the North Sea, has a population of only 494,000, of whom 395,000 are in the city of Bremen proper. In Land Bremen, the excess of male tuberculosis deaths is not apparent except above the age of 55. In 1947 at all ages there were 209 male tuberculosis deaths

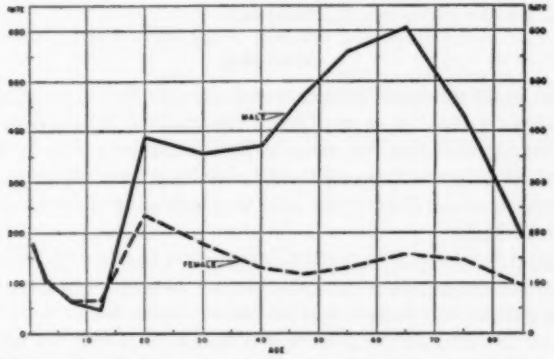

FIG. 5. Death rates for all forms of tuberculosis per 100,000 population, by sex and age, Berlin, 1946.

as against 173 female; the proportion of all deaths ascribed to tuberculosis was 7.4 for males and 7.3 for females.

The tuberculosis experience of Berlin was quite unlike that of the cities in the Western Zone of Germany and more closely resembled that of the cities of eastern Europe, where the rise was catastrophic. The data to be quoted refer to the entire city, not merely the U. S. sector. The trend of mortality has been seen in figure 4. The age distribution of death rates again shows a great excess of adult males over adult females, which is most pronounced over the age of 50 (figure 5). From age 30 upward there were 3,953 male tuberculosis deaths in Berlin in 1947 as against 1,737 female. Why Berlin suffered so heavily is not entirely clear. Certain reasons may, however, be advanced. Berlin had a higher rate than other large German cities before the war; bombing was continuous rather than sporadic; food shortages were presumably greater because of the difficulty of a large city in procuring food from the surrounding farmland; and Berlin was cut off from the use of its sanatoriums, most of which were outside the

city, to a greater degree than other places. Berlin's population is older than in other parts of Germany; with the present age distribution of deaths, this in itself would tend to make the crude death rate somewhat higher.

The relative frequency of pulmonary and other forms of tuberculosis as causes of death showed no remarkable variation in the areas studied, pulmonary tuberculosis ranging from 91 per cent of all tuberculosis deaths in Berlin down to 82 per cent in Hesse in 1947. For the three principal Länder in the U. S. Zone, 85 per cent of the mortality was ascribed to pulmonary tuberculosis and 15 per cent to tuberculosis of other organs. These proportions are identical with the figures for all Germany over the three year period, 1935–1937.

The proportionate mortality or percentage of all deaths ascribed to tuberculosis, in the three principal Länder of the U. S. Zone averaged 5.8 per cent in 1947. The proportionate mortality for Germany in the period 1935–1937 was 6.0 per cent. The comparable figure for the United States in 1945 (all races) was 3.8 per cent, and for the white race 3.1 per cent.

Morbidity

Reports that tuberculosis is epidemic and uncontrolled in Germany have been largely based upon the rise in morbidity reported by health departments. It has been predicted that this rise must be followed after a time by a rise in mortality. Morbidity figures from all the Länder have been carefully studied, and it was the opinion of the Commision that they probably do not reflect a real increase in tuberculosis.

In the United States relatively little attention is paid to the trend in reported cases of tuberculosis, except as an index of case finding. Case reporting is used primarily for getting the patient and his family under health department supervision, and for assisting in the provision of sanatorium care for the patient and examination of his contacts. Ordinarily too many variables affect the recognition and reporting of the disease to make comparisons of morbidity at different times and in different places meaningful. Most of these variables are operative in Germany, and in addition there are several not encountered in the United States.

The classification of active tuberculosis cases presently employed in German public health practice is rather elaborate, having three categories of respiratory tuberculosis and two categories of nonpulmonary tuberculosis. The three respiratory categories may be briefly described as:

(a) Active respiratory tuberculosis, with demonstrable tubercle bacilli.

(b) Active respiratory tuberculosis, without the demonstration of tubercle bacilli but with lesions which are regarded as "open" or infectious. Terms sometimes used for this group are "clinically open" or "facultative open".

(c) Active "closed" or "noninfectious" respiratory tuberculosis. This group includes stationary infiltrations, hilar and bronchial node enlargements, miliary strand-like lesions of lungs, exudative pleurisy, productive cirrhotic lesions, and infants with positive tuberculin reactions.

Most of the types of disease in group (c) would not ordinarily be reported in

the United States. In the absence of knowledge of how large a proportion they constitute, it is felt that this group is best excluded from consideration in the analysis of morbidity.

Morbidity figures from Germany are based upon reports rendered by the tuberculosis clinics or Fürsorgestellen, in which nearly all known cases are registered and where most of the diagnoses are checked and confirmed. In this respect they are more reliable than American data. There are, however, two important factors operating to cause an apparent increase in morbidity. The first of these is the fact that tuberculosis cases are authorized to receive supplementary food rations. This would appear to create an incentive for physicians to report borderline cases and for patients to seek medical care.

The second, and more important factor, is the greatly increased employment of case finding techniques. During and immediately after the war the Fürsor-

TABLE 2A

Initial Examinations and Diagnoses in Bavarian Fürsorgestellen in 1947, by Quarters

PERIOD	INITIAL EXAMINATIONS MADE	NEW CASES OF ACTIVE PULMONARY TUBERCULOSIS REPORTED		CASES PER 100 EXAMINATIONS	
		"Open"	"Closed"	"Open"	"Closed"
January to March	40,277	1,663	4,367	4.1	10.8
April to June	56,684	2,258	6,624	4.0	11.7
July to September	61,437	1,937	5,781	3.2	9.4
October to December	58,956	1,618	5,940	2.7	10.1

Note: "New cases" does not include those cases previously registered with the Fürsorgestellen as "closed" or inactive tuberculosis and subsequently transferred to the above groups. Such cases constitute about two-fifths of the total "active open" and one-fifth of the "active closed" cases reported.

gestellen were unable to operate effectively; but during 1946 and 1947 their case finding activities have been greatly intensified. Fluoroscopy is very widely used in Germany as a diagnostic procedure, the use of roentgenograms being often reserved for cases in which fluoroscopic examination has given positive or suspicious findings, and German physicians are highly skilled in this technique. Records are kept of the number of fluoroscopic examinations per month made by the Fürsorgestellen, and the use of the procedure has increased greatly during the past two years. The larger the number of persons examined, the higher will be the yield of new cases of tuberculosis, although the yield per 100 examinations may diminish. This is illustrated by table 2A in which the number of initial clinic examinations in all the Fürsorgestellen of Bavaria during 1947 is related to the total number of new cases of open and closed active pulmonary tuberculosis reported by the same agencies. While the number of examinations increased up to the third quarter, the number of new cases identified failed to increase proportionately, and in fact there was a definite downward trend over the year in the yield of "open" cases in relation to the number of examinations for tubercu-

losis. Table 2B gives data from the same source for an eighteen month period ending in June, 1948, showing total examinations and total cases of open tuberculosis.

In most of the other areas studied it can be shown that such increases in new cases as have occurred have been in "closed" cases (see category (c) above). One cannot avoid looking with some skepticism on this increase, which means either that a change is occurring in the character of the tuberculosis cases which come to light, or that something is happening to bring the "closed" cases to light relatively more often than formerly. Possible explanations for such a rise are the

TABLE 2B

Total Examinations in Bavarian Fürsorgestellen and Cases of Open Tuberculosis, by Quarters, January 1947 to June 1948

PERIOD	TOTAL EXAMINATIONS MADE	"OPEN" PULMONARY TUBERCULOSIS CASES REPORTED*	CASES PER 100 EXAMINATIONS
January to March, 1947	81,180	2,706	3.3
April to June, 1947	109,052	3,508	3.2
July to September, 1947	112,994	3,152	2.8
October to December, 1947	112,294	2,813	2.5
January to March, 1948	128,341	3,140	2.4
April to June 1948	136,923	3,565	2.6

* Includes all cases of bacteriologically or clinically "open" pulmonary tuberculosis diagnosed during the quarter.

TABLE 3

Total Cases of Tuberculosis Registered at Fürsorgestellen in Berlin in 1947, by Quarters.

	ACTIVE "OPEN" PULMONARY		ACTIVE "CLOSED" PULMONARY	EXTRAPULMONARY
	BACT. POS.	BACT. NEG.		
January, 1947	11,895	9,185	43,850	6,433
April	11,795	9,626	46,980	7,156
July	11,609	9,768	48,559	7,842
October	11,820	9,972	51,272	8,431
January, 1948	11,241	9,760	49,188	8,707

improvements in diagnostic techniques and the incentive to report this type of case.

Another measure of the tuberculosis problem, which also is not employed as such in this country, is the prevalence of the disease as determined from the total number of cases registered with the health departments. Obviously, this is influenced not only by current case finding but also by the efficiency with which old cases are removed from the register after death, moving away, or recovery. It was not possible to ascertain how carefully the registers were maintained, although a very favorable impression was gained of the methodical and precise methods of record keeping and character of nursing supervision in the few clinics visited. The number of registered cases in Berlin by quarters over a period of one year ending in January, 1948 is shown in table 3. There has been an actual

decline in the number of bacteriologically positive pulmonary cases and an equivalent increase in bacteriologically negative "open" cases; a definite increase in the "closed" cases; and a rather marked increase in extrapulmonary tuberculosis. The reason for the latter increase is not known; it may perhaps, as some have suggested, indicate a real increase in chronic extrapulmonary forms which has not yet been reflected in a rising mortality. These figures, however, do not substantiate a real increase in clinically significant pulmonary tuberculosis.

Conditions in the British Zone of Germany have been analyzed in a report by Daniels and Hart (5). These workers obtained findings very similar to those which have been presented above and their conclusions are substantially the same as ours. So far as tuberculosis is concerned there is evidently little difference between conditions in the British and U. S. Zones.

Tuberculosis Control Program

Space does not permit a detailed discussion of the tuberculosis control program. In brief, with American assistance, bed provisions have been greatly increased until now the number of hospital and sanatorium beds per annual death, except in Berlin, approaches the present ratio in the United States. There are still, however, too few beds to meet the accepted standards, particularly in Berlin, and many open cases must be cared for at home. Local public health organizations appear to be doing an aggressive and effective job of case finding and case supervision. A BCG vaccination program has been undertaken under the supervision of the Danish Red Cross. Food supplements are authorized for tuberculous persons, which on the whole provide an adequate dietary for this group when the food can be obtained. Germany is greatly handicapped by an extreme shortage of many essential materials in addition to food, ranging from soap to X-ray film. Only general economic recovery can help this situation, and indeed the whole tuberculosis problem is closely linked to the economic state of the country.

SUMMARY AND CONCLUSIONS

1. Tuberculosis mortality in the U. S. Zone of Germany began to rise promptly at the beginning of World War II, reached a peak in 1945 and has progressively declined in 1946 and 1947. It is still above the prewar level in most places and is well above the rate to have been expected if the prewar downward trend had continued. The extent of the rise was only moderate as compared with that in several other European nations.

2. The increase in mortality appears to have affected infants of both sexes and, to an even greater degree, adult males. Females above the age of one year showed little increase as judged by age- and sex-specific rates for 1946. This is in contrast with the rise in World War I, in which both sexes and all age groups participated. The reason for the difference is not apparent.

3. Case finding programs have been steadily improved and intensified since the resumption of public health activities. This factor and others which have been discussed are believed to be responsible for the apparent postwar increase in tuberculosis incidence. No convincing evidence has been found for a real increase in the incidence of active open pulmonary tuberculosis over the past two

years. The outlook appears hopeful for continued reduction in tuberculosis, barring fresh economic or military disaster.

SUMARIO Y CONCLUSIONES

Tuberculosis en la Población Alemana de la Zona Estadounidense de Alemania

1. La mortalidad tuberculosa en la Zona Estadounidense de Alemania comenzó a elevarse poco después del comienzo de la Guerra Mundial II, alcanzó su acmé en 1943 y ha bajado gradualmente en 1946 y 1947. Todavía supera la cifra preguerra en la mayor parte de los sitios, hallándose bien por encima del coeficiente que hubiera cabido esperar, de haber continuado la tendencia descendente de antes de la guerra.

2. El aumento de la mortalidad parece haber afectado a las criaturas de ambos sexos, y aun más, a los varones adultos. Las hembras de más de un año revelaron poco aumento, a juzgar por los coeficientes específicos por edad y por sexo para 1946, lo cual contrasta con el aumento en la Guerra Mundial I, en el cual participaron ambos sexos y todos los grupos etarios. La causa de la diferencia no es evidente.

3. Las obras de descubrimiento de casos han sido mejoradas e intensificadas constantemente desde que se reanudaron los trabajos de sanidad. Estas obras y otros factores pasan por ser la causa del aparente aumento de la incidencia tuberculosa después de la guerra. No se han encontrado pruebas convincentes de un aumento real de la incidencia de la tuberculosis pulmonar abierta activa durante los dos últimos años. De no sobrevenir nuevos desastres económicos o militares, cabe esperar que continue la disminución de la tuberculosis.

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WHAT DOES A ROENTGENOGRAPHIC SURVEY TEACH THE PUBLIC?

Including a Comparison with Other Tuberculosis Information Polls

CLAUDIA B. GALIHER AND JEANNE E. WRIGHT

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INTRODUCTION

Case finding is of vital importance in a tuberculosis control program. Mass roentgenographic surveys accompanied by a large scale educational program have become more and more the order of the day. The results of such projects in terms of numbers are easy to measure. Educational results are not. Frequently, when the numbers examined roentgenographically do not reach expectations, the statement will be made that, no matter what the numbers examined, the mass study was an effective health education campaign and the people learned a lot about tuberculosis. The Montgomery County Tuberculosis Association resolved to find out whether such is in fact the case.

A committee was formed, consisting of C. Mayhew Derryberry, Ph.D., Chief, Office of Health Education, U. S. Public Health Service; Mrs. Leona Culp, Special Consultant, Office of Health Education, U. S. Public Health Service; K. Frederick Welte, M.D., Director of Tuberculosis, Montgomery County Health Department; Mrs. Jane A. Shepherd, Director, Public Opinion Poll, Washington Post; Miss Claudia Galiher, Executive Secretary, Montgomery County Tuberculosis Association; and Miss Stella Randolph, Director, Public Health Education, Montgomery County Health Department. Technical advice on the sampling was obtained from Mr. Walter Perkins, Statistician with the Statistics and Analysis Division, Bureau of Public Assistance, Social Security Board.

The committee decided to poll a sample of the county two months in advance of roentgenographic survey and to repeat the same poll on a similar sample of the same area just two months after the conclusion of the survey. The Montgomery County chest roentgenographic survey was conducted simultaneously with the District of Columbia Survey, so that Montgomery County people were doubly barraged with information about tuberculosis and chest roentgenograms.

The first poll was conducted in October, 1947. The Montgomery County chest roentgenographic survey lasted from January to March, 1948, during which time two machines were in constant operation and an intensive educational campaign was put on. The second poll was accomplished in May, 1948.

An educational campaign was carried out, based on organizing the entire community to participate in the project. Plans were formulated in such a way as to involve as many groups and individuals as possible. Volunteer committees worked on over-all planning, locations and hours, a speaking program to reach all organized groups, the recruitment of volunteer clerical personnel to work with the roentgenographic units, distribution of posters, a house to house canvass, special roentgenographic arrangements for businesses. Newspapers, radio, thea-

ters, schools, and churches all played an important part in spreading information concerning the survey.

The objectives of the study were broadened from a measurement of a particular educational project to include the obtaining of information for program planning purposes, so that, as finally stated, the objectives were:

(*1*) To test the accomplishments of the educational program of the tuberculosis association in one campaign between October, 1947 and May, 1948.

(*2*) To provide information concerning people's knowledge of and attitude toward tuberculosis, which will be useful to the tuberculosis association in carrying out its educational program.

The Questionnaire

A questionnaire was developed by the committee named above. All the questions were designed for free responses on the part of the persons interviewed, in order not to suggest possible answers and thereby introduce bias into the study. For purposes of comparison a number of questions previously used in a Gallup Poll were incorporated. The questionnaire was tested and revised before being printed and put into use.

The questions covered the following areas: (*a*) the cause and communicability of tuberculosis; (*b*) the cure for tuberculosis; (*c*) symptoms in tuberculosis; (*d*) the value of roentgenographic examination, and for whom; (*e*) stigma attached to tuberculosis; (*f*) attitude toward people who have had or who have tuberculosis; (*g*) personal responsibility in the control of tuberculosis; (*h*) personal acquaintance with tuberculosis, especially in family situations; (*i*) exposure to tuberculosis education.

THE INTERVIEWERS

Volunteer interviewers were obtained from the area in which the poll was to be taken and came primarily from a group of women interested in and active in the local Health Center.[1] These women all attended a training session at which the purpose of the poll was carefully outlined, the selection of the sample explained, the composition of the questionnaire gone over, and interviewing technique and recording carefully explained. Sample interviews were presented for illustrative purposes. Interviewers were impressed with the importance of carrying out the instructions given them in order not to impair the significance of the study.

THE SAMPLE

Silver Spring, Maryland, was selected as the portion of Montgomery County in which the poll would be conducted, since it has the greatest concentration of people in the county and also because it is an area in which there is great economic differentiation.

The sample was carefully chosen on a household basis. This system was used to cut down the bias occurring when interviewers are allowed to choose their own respondents. Also, it automatically gives an accurate sample by economic status, as homes are chosen from all parts of town. The area to be polled was

[1] Silver Spring Public Health Lay Committee.

marked on a map, and each block in the area was assigned a number. Then one out of every four blocks was picked at random, using J. H. C. Tippett, Random Sampling numbers. Within each of the selected "random" blocks, every sixth household unit was taken, starting alternately at the north, east, south, and west corners. Thus, block 1 was used, representing the first four blocks, the first household, starting at the north corner; block 7 from the second four blocks, the second household, starting at the east corner; block 12 from the third four blocks, the third household from the south corner, et cetera. Three hundred five addresses were obtained in this manner for the first sample. The second sample of 332 addresses was obtained in a similar manner. The blocks used in the first sample were excluded from the second, so that the opinion poll itself would not

TABLE 1

Composition of Samples

	POLL 1 (297 INTERVIEWS)	POLL 2 (326 INTERVIEWEES)
	Per cent	Per cent
Total interviews	100	100
Both sexes	100	100
Male	30	32
Female	70	68
All ages	100	100
Under 30	33	29
30 to 44	44	46
45 and over	22	24
Unknown	1	1
All educational levels	100	100
School	13	9
High school	50	52
College	35	38
Unknown	2	1

affect the results. Volunteers were given specific household addresses. Each volunteer had approximately 10 interviews.

Substitutions were discouraged and specific instructions were issued as to how they should be made, if necessary. Approximately the same number of men and women were to be interviewed. The lowest age acceptable was 15 years, the same group as was eligible for a chest roentgenogram in the survey. The age of the respondents was to be recorded on the schedule according to the guessed observation of the interviewer.

Two hundred ninety-seven (297) interviews were obtained in sample 1, and 326 in sample 2. The difference between the number of addresses obtained and the number of interviews made is a consequence of refusals and the fact that in some areas homes had been vacated to make room for the expanding business section of the town.

The age and educational distribution of the samples is believed to be similar to that of the population of Silver Spring but no accurate figures are available on

the composition of the population at this time. The 1940 census figures on the population of Montgomery County show an older and a less highly educated group. There is reason to believe, however, that Silver Spring, a city that is largely a suburb of Washington, D. C., and which grew rapidly during the war, is made up of a younger, better educated group than that reported in 1940 for the whole of Montgomery County. The sex distribution in the sample is definitely at variance with the existing population. It is likely that there are slightly more women than men in the area, but the preponderance of female interviews is probably a result of the fact that women were more readily available at home. This result was obtained in spite of instructions to interviewers to try to obtain half men and half women in their interviews. This has apparently made little difference to the sample, as the amount of knowledge held by men and women regarding tuberculosis was similar.

RESPONSES

A tabulation was made of the questions asked. Here the questions have been rearranged by subject matter for ease of presentation. In the interview the questions were carefully placed to minimize the influence of one question upon the answer to another.

The Cause and Communicability of Tuberculosis

The following questions were asked in order to determine what ideas people have as to the cause of tuberculosis and whether or not they think it is catching:

(*1*) *"What do you think is the cause of tuberculosis?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Germs	21	26
Undernourishment or malnutrition	25	30
Neglect of health	21	17
Run-down condition or low vitality	26	26
Living conditions	19	17
Heredity	12	8
Don't know	5	14
Other	12	8

There seems to be great confusion among the respondents with regard to the cause of tuberculosis. The so-called contributory factors, malnutrition, neglect of health, and run-down condition were indicated as often as germs. Recognition of the frequent accompanying factors of disease as a basis for social action is important in a broad community-prevention program. One-tenth of the respondents mistakenly named heredity as the cause. The responses add up to more than 100 per cent, as each person was allowed several responses.

There was a slight improvement in people's knowledge between the two samples. In the second poll five per cent more mentioned germs, 4 per cent less mentioned heredity. An interesting phenomenon occurred with the "don't know's." The percentage so responding was 5 per cent on sample 1 and 14 per cent on sample 2. It may be that persons having fixed erroneous ideas experience feelings of doubt when confronted with "facts."

(2) *"Do you think tuberculosis is catching?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Yes	84	85
No	11	9
Don't know	5	6

In spite of confusion as to the specific cause of tuberculosis, the great majority of people realize that it is a contagious disease.

(3) *"Do you think a baby can be born with tuberculosis?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Yes	36	34
No	42	40
Don't know	22	26

The situation regarding heredity and tuberculosis, as reflected in the first question, is not absolute, inasmuch as, when directly asked if a baby can be born with tuberculosis, over one-third replied "yes."

(4) *"How about yourself? In your opinion is it possible for you to get tuberculosis, or do you feel safe from this disease?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Possible	68	76
Safe	31	22
Because older people safe	8	4
Recently or periodically checked	6	7
No tuberculosis in family	4	4
Am healthy	7	4
Other	6	3
Don't know	1	2

Generally speaking, people do realize that it is possible for them to get tuberculosis; 8 per cent more felt that way after the roentgenographic survey. There was a definite decrease in the percentage of older people who feel safe because of their age, a change which was not reflected in a change in the sample.

The Cure for Tuberculosis

The following questions were asked to determine whether or not people think tuberculosis is a curable disease, and what their ideas are with respect to the cure:

(1) *"Do you think a person who has tuberculosis can get well?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Yes	95	95
No	4	2
Don't know	1	3

On both tests an overwhelming majority indicated that they thought tuberculosis was curable.

(2) *"What do you think a person who has tuberculosis should do to get well?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Rest in bed	38	33
Good food	21	21
Proper medical care	61	67
Go to hospital	24	20
Fresh air	11	10
Proper climate	11	10
Other	7	4

The majority were aware of the importance of proper medical care. Rest in bed, good food, and sanatorium care were also recognized. Unfortunately, climate is still held as important in the cure of tuberculosis by 10 per cent of the people. It is probable that, had a direct question on climate been included, a larger percentage would have thought it important. These responses add to more than 100 per cent as multiple answers were permitted. Not one person on either poll indicated the use of drugs or medicine.

Symptoms in Tuberculosis

This question was asked to determine people's awareness of the absence of symptoms in early tuberculosis:

"In your opinion, when a person first gets tuberculosis, does he feel all right or does he have definite symptoms?"

	Per cent of Responses	
	Poll 1	*Poll 2*
All right	46	48
Symptoms	43	40
Don't know	11	12

Less than one-half of the people questioned in each sample were aware that early tuberculosis may exist without symptoms. There was little change between poll 1 and poll 2, in spite of the fact that great emphasis was placed upon this point during the survey.

Age and the Occurrence of Tuberculosis

This question was asked to determine to what extent people were aware of tuberculosis as primarily an adult problem, and particularly a problem of the most productive years:

"As far as you know, at what age is tuberculosis most common?"

	Per cent of Responses	
	Poll 1	*Poll 2*
Under 5	6	3
5 to 14	18	13
15 to 44	73	80
45 and over	9	7
Don't know	11	10

Responses to this question were recorded in terms of any or all age groups indi-

cated, so that the percentages add to more than 100. Most respondents were more aware of ages which fell, for recording purposes, in the 15 to 44 group than any other, *e.g.*, an answer of "the twenties" would be in this group. A lack of correct knowledge is shown by the number who indicated ages under 15 and by the very small number who indicated ages over 45.

The Value of Roentgenographic Examination

The following questions were designed to gather people's ideas regarding roentgenographic examination and its application:

(*1*) *"As far as you know, does the doctor have to have an X-ray before he can be sure that a person does not have tuberculosis or can he tell by a physical examination?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
X-ray	69	68
Physical examination	12	10
Both	11	10
Don't know	8	12

About seven of ten persons think that roentgenographic examination is necessary before tuberculosis can be excluded. One of ten thinks that the doctor can tell by physical examination without a roentgenogram. Those who answered "both" were probably avoiding the issue, and fall for the most part into "don't know."

(*2*) *"Which is more important, would you say, for parents to be X-rayed, or for their young children to be X-rayed?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Parents	31	49
Children	26	13
Both	41	36
Don't know	2	2

There was a marked improvement on this question. This was one of the most stressed points during the survey. Emphasis was placed on the fact that only persons 15 years of age or over were to have roentgenograms. Some children were even turned away from the machines.

(*3*) *"Do you personally feel it important for everyone to be X-rayed?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Yes	81	96
Once a year	39	51
Periodically, but less often	25	27
As often as necessary	6	11
Don't know	11	7
No	15	3
Don't know	4	1

The survey undoubtedly convinced many people of the importance of roentgenographic examination. The per cent so responding jumped from 81 on poll 1 to 96 on poll 2. Approximately half the people on poll 2 thought people should be X-rayed once a year.

(4) *"Have you ever had an X-ray of your chest?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Yes	64	89
Within year	20	65
1 to 5 years ago	28	18
Over 5 years ago	13	5
Don't know	3	1
No	36	11

This question might be considered to give an index to the response of the community to the roentgenographic survey. The above findings indicate that 89 per cent of the people in Silver Spring have had chest roentgenograms, all but 5 or 6 per cent within the last five years; 65 per cent (those who have been examined within the last year) were probably examined roentgenographically in the course of the survey.

Social Stigma of Tuberculosis

This question was designed to determine to what extent people feel that tuberculosis is something of which to be ashamed:

"If someone in your family had tuberculosis, would you feel free to talk about it or would you want to keep it to yourself?"

	Per cent of Responses	
	Poll 1	*Poll 2*
Talk	80	80
Keep to self	15	15
No one else's business	5	7
Fear of social stigma	4	3
Shunning of contagious individual	4	4
Other	2	1
Don't know	5	5

It is interesting to note that there is no change in people's ideas regarding how freely they would talk about someone in their family having tuberculosis. Fifteen per cent of the people would keep such information to themselves and 5 per cent don't know whether they would or not. One person in thirty still feels a stigma attached to tuberculosis. The others who wouldn't talk gave reasons such as "no one else's business," "a matter between the individual and his doctor," and a fear of "shunning of the individual" because of the contagious nature of the disease.

Attitude toward People with Arrested Tuberculosis and Active Tuberculosis

The following questions were asked to determine people's attitude toward associating with persons in these two categories:

(1) *"Suppose one of the people you worked with, you learned one day, has spent some months in a hospital with tuberculosis but has been released by the doctor and is able to work. What would you think about this?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Situation all right	84	82
Situation bad but would do nothing	3	5
Sufficiently disturbed to check up on self or urge that something be done about the situation	13	13

Most people would feel no danger attached to associating with people who have been cured. However, one person in eight would react unfavorably.

(*2*) *"Suppose you had a job and you suddenly found out you were working right alongside a person who actually has tuberculosis. What would you do in this situation?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Nothing	10	7
Speak to employee	22	25
Report to employer	24	25
Avoid, or change jobs	23	26
Have check-up	22	23
Other	13	10

Most people would take action of some kind to improve the situation when closely associated in a working relationship with someone who has tuberculosis. However, the 7 per cent on poll 2 who would do nothing is still far too large.

Personal Responsibility in the Control of Tuberculosis

The following questions were included in the questionnaire to gather information as to the respondents' feeling of responsibility in a community-control program.

(*1*) *"A man you know had a chest X-ray at his office. He was sure he was in good condition. Later he received first one and then another letter from the Health Department asking him to come see the doctor. He became very much annoyed and told his friends that his health was none of the Health Department's business and that he was not going to see their doctor. What do you think of his course of action?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
His attitude bad	94	97
His attitude all right	6	3

In this question a situation was presented in which the person concerned might or might not have tuberculosis, but is uncooperative. It was hoped that the responses would indicate an individual's own response to a similar situation. The majority felt that his attitude is definitely undesirable, with a slight improvement between polls. It may be that the small per cent who concur in his action would be uncooperative if patients themselves.

(*2*) *"Suppose a close friend of yours came to you and told you that for no definite reason she was afraid she might have tuberculosis. What would you advise her to do?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Have medical check-up or X-ray	96	96
Nothing	4	4

This question was designed, not only to discover what course of action an individual would advise for a friend who thought she might have tuberculosis, but in the hope that a conclusion might be drawn as to what he might do himself. An overwhelming majority would seek medical advice or have a chest roentgenogram, and no change was reflected between the polls.

(3) *"In chest X-ray surveys about 60 per cent of the people come and have an X-ray. What do you think is the main reason why the other 40 per cent do not?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Neglect or carelessness	48	61
Fear	25	24
Think they are all right	27	16
Don't know	4	4
Other	12	9

This question was designed to gather information as to reasons why roentgenographic surveys are not 100 per cent successful. It was hoped to determine from these responses to what degree people stay away from survey machines from fear. One-fourth of the respondents seem to feel fear a pertient factor. The main reason, however, is neglect or carelessness. There was a slight shift from "think they're all right," which might reflect an opinion that that is not a good reason for staying away.

(4) *"If an X-ray survey were to take place here, would you go and have a chest X-ray?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Yes	82	83
No	18	17
Am checked periodically	6	7
Physically unable to go	1	1
Not in favor	1	1
Too old to be worth while	3	2
Feel fine	4	1
Other	3	5

The results obtained through questioning respondents with regard to participation in a proposed roentgenographic survey were approximately the same on both polls, as were the reasons for not participating. Comparing this figure to the 96 per cent who think it important for everyone to be examined roentgenographically, it would seem that some of the 96 per cent feel that everyone but they should be so examined.

(5) *"Do you think that tuberculosis is an important problem in this community?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Yes	76	82
No	13	11
Don't know	11	7

This question was designed as a warm-up question, and was the first asked in each interview. Apparently, having a roentgenographic survey was sufficient proof for some that tuberculosis was important.

Personal Acquaintance with Tuberculosis

This question was asked to determine what percentage of the people have tuberculosis in their families or in close friends. It was hoped to find out whether the knowledge and attitude of those with tuberculosis in their families differed from that of the rest of the sample.

(*1*) *"Has anyone in your immediate family or a close friend ever had tuberculosis?"*

	Per cent of Responses	
	Poll 1	*Poll 2*
Immediate family	21	18
Close friend	17	16

One of every five respondents reported the existence of tuberculosis in their families at some time. It is possible that this figure might be even higher, for some of those with tuberculosis in their families might fall in the group which would "keep it to self."

SCORES

In order to compare the amount of knowledge of the various groups within the community and to evaluate the results of the educational campaign which took place in the course of the roentgenographic survey in Montgomery County, a system of scoring the tests was devised. The scoring is not intended to reflect the absolute level of knowledge held by Silver Spring. Another questionnaire or another scoring method would yield different results. The same method of scoring was used in both polls. The scores, by sex, on the two polls were as follows:

	Average Score	
	Poll 1	*Poll 2*
Both sexes	72.0	74.3
Male	72.2	72.4
Female	71.9	75.2

From the above it can be noted that there is only a slight increase in the average scores of poll 2 over poll 1, not more than might be attributable to a change in sample. It can further be noted that, while the degree of knowledge held by men and women appears the same on poll 1, there is a slight difference in favor of the females on poll 2 and that, if there has been any increase in knowledge, it is among the women.

The results were examined in terms of age groups:

	Average Score	
	Poll 1	*Poll 2*
All age groups	72.0	74.3
Under 30	75.5	74.7
30 to 44	73.5	76.2
45 and over	63.5	70.1

In the first sample the greatest amount of knowledge was held by persons under 30; the oldest age group was well below the average. In the second poll the 30 to 44 group were best informed, and the older people again lag. It is in the

45-and-over age group, however, that the greatest improvement between the polls occurs, the 30 to 44 group showing the next best improvement. The score of the under 30's has dropped slightly, but the difference is so small that it is almost certainly due to a difference in the sample.

Classified by the level of education, the results were:

	Average Score	
	Poll 1	*Poll 2*
All groups	72.0	74.3
School	63.6	71.5
High school	70.9	72.5
College	77.3	77.7

The knowledge regarding tuberculosis varied directly with the amount of education. Since tuberculosis education is not normally a part of elementary school education, however, and is usually given at high school and college levels, one might expect even more disparity. It would appear that, although knowledge regarding tuberculosis increases with education, other sources of information would appear to be at least equally important. Comparing the scores attained by the least educated group on the two polls, it is seen that the greatest improvement in knowledge occurred in this educational group. Perhaps this group recognizes that it does not know and is willing to learn.

If experience is the best teacher, one would expect people from families in which there has been tuberculosis to know more than the average person.

	Average Score	
	Poll 1	*Poll 2*
All groups	72.0	74.3
Those with tuberculosis in family	70.5	76.4
Those with no tuberculosis in family	72.3	73.8

Before the roentgenographic survey, the people with tuberculosis in their families were slightly below the average. After the survey, however, they were well above the average, their score having jumped 6 per cent, as compared to about 1½ per cent for the people with no tuberculosis in their families. This would seem to indicate that people with tuberculosis in their families, who have reason to be especially interested, learn more than the average when confronted with the opportunity to find out the true facts.

EXPOSURE TO TUBERCULOSIS EDUCATION

The respondents were asked the following series of questions to determine to what educational media regarding tuberculosis they had been exposed and to attempt to discover their relative values. The following table shows the per cent of the people exposed to the various media.

	Per cent of Responses	
	Poll 1	*Poll 2*
Have you ever read about tuberculosis in the newspaper? Yes	90	96
Have you ever seen any pamphlets or posters on tuberculosis? Yes	82	91
Have you ever heard anything about tuberculosis on the radio? Yes	77	86
Have you ever seen a moving picture on tuberculosis? Yes	34	43
Have you ever heard anyone talk or speak at a meeting on tuberculosis? Yes	27	37

During the course of the survey more people were reached with information on tuberculosis than had been reached before. The importance of the various media with respect to coverage was in this order: newspaper, pamphlets or posters, radio, moving pictures, speakers.

An evaluation of the various media was difficult to accomplish, as most people were exposed to several sources of information, and quite a few to all. However, consideration of the accomplishments of the various media in terms of scores attained on poll 2, shows the various media to be effective in this order: speakers, movies, radio, posters or pamphlets, newspapers. It would seem that the more personal approach is the more effective.

COMPARISON WITH OTHER POLLS

Public opinion polls are very popular today, not only for purposes of evaluation, but also as a part of basic planning. Some comparison with other polls recently completed would seem valuable.

During 1947, public opinion polls on tuberculosis were conducted by the American Institute of Public Opinion (Gallup Poll)[2] operating over the entire country, and in the following cities under various auspices, including tuberculosis associations: Hartford, Connecticut[3]; Denver, Colorado[4]; and Mishawaka, Indiana[5]. The questions used on the various polls are quite similar, and in some instances identical.

Comparable questions for the most part received similar answers in all of the polls. For example: "Do you think tuberculosis is catching?"

Polls	*Per cent answering "yes"*
Gallup	70
Hartford	80[6]
Denver	80[6]
Mishawaka	70
Silver Spring Poll 1	84
Silver Spring Poll 2	85

Silver Spring was somewhat better informed on this particular question than were the others reported above. This may be a consequence of the composition of the city, the citizens of which on the whole are well educated and high in economic status.

Questions on the possibility of inheriting tuberculosis were asked in all of the polls. "*Do you think a baby can be born with tuberculosis?*" or "*Do you believe that tuberculosis is inherited?*" brought the following responses:

[2] George Gallup, The Gallup Poll, as reported in the Washington Post, June 7, 1947, page 9.

[3] Chas. E. Lyght, Public Opinion Poll on Tuberculosis to aid Hartford Assn. in Revising Program, the NTA Bulletin, February, 1948, page 29.

[4] Chas. E. Lyght, Denver to Use Findings of Tuberculosis Poll to Strengthen and Extend Program, The NTA Bulletin, April, 1948, page 61.

[5] Cyril J. Hoyt, John Q. Public Attitudes affecting Tuberculosis Control, Monthly Bulletin, Indiana State Board of Health, June, 1948, page 128.

[6] The published figures are "8 out of 10."

Polls	Per cent answering "no"
Gallup	35
Hartford	30
Denver	40[7]
Mishawaka	43
Silver Spring Poll 1	42
Silver Spring Poll 2	40

People everywhere were poorly informed on this subject of the inheritability of tuberculosis.

A great discrepancy is seen in the answers to the question regarding the cause of tuberculosis. When asked "*What do you think is the cause of tuberculosis?*" as the third question in the Silver Spring poll (the first two questions were "*Do you think tuberculosis is an important problem in this community?*" and "*Why?*") only 21 per cent on poll 1 and 26 per cent on poll 2 gave "germs" as the answer. The Gallup Poll results were similar, with a 22 per cent response of "germs." Reports from Hartford and Denver, however, indicate that at least two-thirds of their people knew that germs caused tuberculosis. It is interesting to consider why this difference exists. Is it that the people of Hartford and Denver are acutely aware of germs as the causative agent of tuberculosis? Was the response in some way connected with the way in which the question was worded or placed? Has the educational program in these two cities been so far above the country as a whole to make this difference? These are just a few questions in which the clue might be hidden. Different arrangement of questions might well bring different responses. For example, if this particular question were preceded by "*Do you think tuberculosis is catching?*" the interviewer might be considered to have inserted the idea of a causative agent in the respondent's mind.

Most people believe that a person can recover from tuberculosis, as seen by the percentages so reporting in the various polls:

Polls	Per cent answering "cure possible"
Gallup	83
Hartford	90[8]
Denver	75[9]
Silver Spring Polls 1 and 2	95

The citizens of Silver Spring appear to have a more optimistic outlook than the others.

Somewhat comparable questions were asked in Mishawaka and Silver Spring to determine people's attitudes toward the person with arrested tuberculosis. The responses indicate that 78 per cent in Mishawaka and 82 per cent in Silver Spring would be willing to work alongside a person who has recently recovered from tuberculosis. (Denverites generally believed that a person with arrested tuberculosis can resume normal living, only 19 per cent suggesting that an ex-tuberculosis patient would be under extreme restrictions.)

[7] Reported as "about four in ten."
[8] Reported as "9 out of 10."
[9] Reported as "3 out of 4."

On the question of whether or not a person would wish to keep to himself the fact that someone in his family had tuberculosis, reports are available only from Mishawaka and Silver Spring.

Polls	Per cent feeling free to talk
Mishawaka	82
Silver Spring Polls 1 and 2	80

"Feeling all right" as opposed to "symptoms in early tuberculosis" brought similar low responses from Mishawaka and Silver Spring.

Polls	Per cent answering "feeling all right"
Mishawaka	43
Silver Spring Poll 1	46
Silver Spring Poll 2	48

The degree of popular acceptance of the roentgenographic survey as an instrument in tuberculosis control might be measured by the willingness of persons to be examined in a roentgenographic survey if one were to take place.

Polls	Per cent answering "would be X-rayed"
Mishawaka	86
Silver Spring Poll 1	82
Silver Spring Poll 2	83

It would appear that the campaign to examine all adults in the United States is making headway, as reflected by the following:

Polls	Per cent who have been X-rayed
Gallup	42
Hartford	47
Denver	63
Mishawaka	57
Silver Spring Poll 1	64
Silver Spring Poll 2	89

The above responses probably reflect the extent to which opportunity has been afforded the various populations to have a chest roentgenogram.

COMMENT

The results of this study indicate that people's attitudes are, for the most part, constructive, and that the general level of knowledge is encouragingly high, expecially in regard to the contagious nature of tuberculosis and the fact that it can be cured. The great knowledge deficiencies concerned the inheritability of tuberculosis, the lack of symptoms in early tuberculosis, climate as a factor in the cure of tuberculosis, and the amount of tuberculosis in older age groups.

It was desired to find out, not only what misconceptions the people might have, but in what population groups the level of knowledge was lowest. The following generalities can be stated:

(*1*) Men and women have approximately the same degree of knowledge.

(*2*) Older people are less well informed than their younger neighbors.

(3) College people are better informed than high school people, who are, in turn, better informed than those with only an elementary school education.
(4) Persons with tuberculosis in their families know less than average on poll 1 but more than average on poll 2.

The improvement in people's knowledge during the roentgenographic survey was slight, only 2.3 per cent. However, greater improvement can be noted in some sections of the population and on some of the questions, *e.g.*, in age groups over 45, in persons with grammar school education or less, in persons with tuberculosis in their families, and most notably on questions having to do with roentgenographic examination. The fact that persons with tuberculosis in their families improved in knowledge regarding tuberculosis emphasizes the receptiveness of this group and points up the need for more intensive education.

A comparison was made of the results of the Silver Spring polls with those of similar polls conducted by the Gallup Poll and in the cities of Hartford, Connecticut; Denver, Colorado; and Mishawaka, Indiana. The most striking thing about such a comparison is the similarity of knowledge in these widely separated cities.

It would seem that during a roentgenographic survey, people's ideas about tuberculosis did not change radically, even though their ideas with regard to roentgenographic examinations did. It may be that, if knowledge has been increased in this one area, an important accomplishment has been made. Advertising specialists concentrate on one thing at a time, as an effort to cover a multitude of points accomplishes little. Education is a cumulative experience. To accomplish desirable objectives, tuberculosis education must be continuous.

It seems somewhat difficult to change preconceived ideas. It might even be said that an intermediate step to complete change is one of doubt. This concept would reemphasize the importance of the right idea in the first place and make the school of paramount importance in a community education plan.

Evaluation is an important part of any activity. The results reported above have furnished figures on the level of tuberculosis knowledge in Silver Spring on two different occasions, and have shown what can be expected in increased knowledge through an educational campaign such as accompanied the Montgomery County chest roentgenographic survey. Equally important, the facts are now available to furnish a sound foundation for future program planning.

SUMMARY

Two public opinion polls, one preceding and one following a county-wide chest roentgenographic survey, were conducted in Silver Spring, Maryland, in an attempt to find out what people learn about tuberculosis in the course of a roentgenographic survey. At the same time an attempt was made to obtain information of the people's knowledge and attitude concerning tuberculosis for use in the planning of future programs. Every step, the design of the questionnaire, the selection of the sample, the training of the volunteer interviewers, and the analysis of the responses, was carefully planned and executed in order that the results should be statistically accurate.

The improvement in people's knowledge during the roentgenographic survey was slight, only 2.3 per cent. Nevertheless improvement greater than this was noted in some sections of the population and in the responses to certain questions. Improvement was most evident in age groups over 45, in persons with grammar school education or less, in persons with tuberculosis in their families, and particularly in the answers to questions concerned with roentgenography.

SUMARIO

¿Qué Enseña al Público una Encuesta Radiológica?

Dos censos de la opinión pública, uno antes y otro después de una encuesta radiográfico-torácica en un distrito completo, fueron tomados en Silver Spring, Máryland, E. U. A., tratando de averiguar lo que la gente aprende acerca de la tuberclosis en el curso de una pesquisa radiográfica. Procuróse al mismo tiempo obtener información relativa a los conocimientos y actitud de la gente con respecto a la tuberculosis, con mira a emplear los datos al proyectar obras futuras. A fin de que los resultados fueran estadísticamente exactos, se estudiaron y ejecutaron con cuidado todas las medidas tomadas, el plan del cuestionario, la selección de la muestra, la preparación de los entrevistantes voluntarios y el análisis de las respuestas obtenidas.

El aumento de los conocimientos del público durante la pesquisa radiográfica fué leve: apenas de 2.3 por ciento, aunque se notó un aumento mayor que éste en algunos sectores de la población y en las respuestas a ciertas preguntas. El aumento fué más manifiesto en los grupos de más de 45 años de edad, en las personas con educación primaria o menos, en las que tenían tuberculosis en la familia, y particularmente en las respuestas a las preguntas referentes a roentgenografía.

ORAL PROTEIN HYDROLYSATE IN PULMONARY TUBERCULOSIS

A. A. KINNEAR AND E. N. KEEN[1]

(Received for publication May 13, 1948)

This paper records the results of feeding protein hydrolysate to colored adult males with tuberculosis. Thirty-eight patients were studied in all, 19 were "test" patients and 19 were "control" patients. To preserve random sampling, alternate patients were allotted as "test" patients.

PLAN OF INVESTIGATION

Complete clinical and radiological examinations revealed no evidence of other diseases. The urine of all patients was essentially normal except for one instance of transient albuminuria which later cleared. No evidence of amyloidosis was detected.

"Control" patients and "test" patients alike were submitted to the following procedures:

(*1*) The weight was recorded at 21 day intervals.

(*2*) The daily temperature was routinely recorded.

(*3*) The blood sedimentation rate was determined at 21 day intervals.

(*4*) A roentgenogram of the chest was taken at 21 day intervals.

(*5*) Ten ml. of blood were drawn from an arm vein with minimal constriction, also at 21 day intervals. Of this, 5 ml. were put into a tube with the correct amount of standard Wintrobe anticoagulant mixture. This portion was used to determine the packed cell volume, the hemoglobin concentration and hence the mean corpuscular hemoglobin concentration. The remaining 5 ml. of blood were allowed to clot and the serum separated. Part of this serum was fractionated and the remainder was used for the empiric liver function tests.

Each "test" patient was then given 50 Gm. of protein hydrolysate[2] per day over and above his ordinary hospital diet. This protein hydrolysate yielded 53 per cent protein on triplicate Macro-Kjeldahl determinations. At three weeks from the commencement of feeding and again at six weeks, blood was withdrawn as before and the investigations outlined above were repeated. The unpalatability of the preparation caused no difficulty.

Methods: The erythrocyte sedimentation rate was determined in Westergren tubes and the fall at the end of one hour was corrected for anemia by means of the packed cell volume.

The packed cell volume was determined in a standard Wintrobe (1) tube, after centrifuging for 30 minutes at 3,000 r.p.m.

Hemoglobin was determined by an alkaline hematin method. A Hilger photoelectric absorbiometer was calibrated with the inorganic solution of Gibson and Harrison (2), using a green filter at 530 μ. The resulting graph was used in reading hemoglobin values, estimations of which were done at least twice for each specimen.

[1] From the Union Health Department Laboratories, Cape Town, South Africa.

[2] Carnesco, a brand of protein hydrolysate was kindly made available through the good offices of Dr. B. A. Dormer, Chief Tuberculosis Officer for the Union, and the Natal Branch of the S. A. Red Cross. The formula supplied with the Carnesco A was: meat flour 40 per cent, dried skim milk 40 per cent, sugar 16 per cent, food yeast 4 per cent.

Total serum proteins were estimated after the method of Koch and McMeekin (3), using a Micro-Kjeldahl technique with subsequent nesslerization. Duplicate estimations were made and results differing by more than 0.2 Gm. were discarded.

Serum globulins were precipitated by the method of Howe (4), using 23 per cent sodium sulphate, and an aliquot of the albumin remaining in solution was subjected to a micro-Kjeldahl procedure with nesslerization. As above, duplicate estimations were made and results differing by more than 0.2 Gm. were discarded.

The thymol turbidity test was essentially that of Maclagan (7), using a thymol buffer of pH 7.8 and using the upper limit of normal as 4 Maclagan units.

The serum colloidal gold test (5) used was the modified Mclagan technique (6), using a citrate sol. A buffer of pH 7.7 to 7.8 precluded the necessity for preliminary standardization of the constant particle gold sol.

The modified cephalin cholesterol flocculation test of Hanger (8, 9) was used, using both cephalin prepared in this laboratory and the combined cephalin cholesterol mixture made by Difco Co. No significant differences were noted in comparing the results of the two antigens. The serum for this test was separated without undue exposure to light, as has been emphasized by Neefe (10). Krautman (11) used an alkalized saline solution and found that nonspecific results were kept to a minimum. Alkalized saline (0.85 per cent) was used and positive and negative control sera were tested in each series of determinations.

RESULTS

Intensive study of the clinical records and the chest roentgenograms of the patients in the treated group revealed no measurable effects which could be attributed to the protein hydrolysate.

The results are presented in table 1. Under each heading the first line enumerates the results which fall within generally accepted normal limits. The next line or lines indicate degrees of abnormality as set out on the left. The results for both the "test" and "control" groups are presented in the three columns. The first column indicates the beginning of the survey, the second the middle (after three weeks), and the third, the position at the end of the six weeks survey period. It will be noted that some values are missing from the third column in the control section. This is due to the death of 2 of these patients and the departure of one other. Patients were allotted as far as possible alternately to the "control" and the "test" groups. The only bias entering into the selection was a temptation to choose the more cooperative type of patient for the test group. The results showed that the patients in the "control" group were, from the start, in a poorer nutritional state than those in the "test" group. Since, however, no significant change was recorded in the "test" group over the six weeks' period this fact becomes of less importance. The results have been pooled in order to study some aspects of the nutritional state of patients suffering from pulmonary tuberculosis.

Erythrocyte sedimentation rate: Of 58 patients at the beginning of the survey, 7

had erythrocyte sedimentation rates of 10 mm. or less. This proportion did not significantly alter during the six weeks, and in general, the rate neither altered nor fluctuated to any great extent in patients from either group. Getz, West, and their associates (12) found a positive statistical correlation between the sedimentation rate and the serum albumin level. An opportunity was taken to confirm these findings.

Over a total of 111 observations, a positive correlation of 0.60 was found. The fact that the amount of plasma albumin is one of the factors influencing the rate of clumping and sedimentation of red blood corpuscles was further illustrated by Gray and Mitchell (13), who showed that albumin added to blood with a rapid erythrocyte sedimentation rate slowed the rate down. These results, however, did not rule out the possibility that other protein fractions may have important effects on the sedimentation rate.

Packed cell volume: The proportion of patients (20 of 38) in whom the packed cell volume did not fall below 45 per cent must be compared with the figures for hemoglobin as given below. It would seem to indicate that the tuberculous state has rather less effect on the production of an adequate volume of red cells than it has on hemoglobin metabolism.

Hemoglobin: A hemoglobin concentration of 14 Gm. per 100 ml. was arbitrarily chosen as the lowest normal value. Twenty-four of the 38 patients failed to reach this level. This standard is probably less stringent than that set for packed cell volume and a higher figure would obviously have brought out the difference to a greater extent. Getz, West, and their associates (12) showed that the most constant deficiency finding in a series of adult males with tuberculosis was vitamin C deficiency. After that came hemoglobin deficiency and then plasma protein deficiency, especially in the albumin fraction of the serum protein. The present figures tend to confirm the hemoglobin findings although over one-third of the patients had more than 14 Gm. of hemoglobin per 100 ml. of blood.

Mean corpuscular hemoglobin concentration: As might be expected from the data already presented, the values for the mean corpuscular hemoglobin concentration showed striking reduction. The accepted normal lower limit of hemoglobin saturation is 32 per cent and only two estimations throughout the survey fell at or above this level. A poor hemoglobin concentration can thus be said to be the only consistent finding in all of the patients of this survey and is the point in hemopoiesis which the tuberculous toxemia appears to effect. The anemia produced is of the type classically supposed to result from disorders of iron metabolism resulting in poor hemoglobin synthesis. These patients had adequate iron in their diet and were not subject to repeated hemoptyses. Globin, a protein of the histone class, constitutes about 96 per cent of the hemoglobin molecule and it may be assumed that availability of protein is a necessity in the synthesis of hemoglobin. Orten and Orten (14) studied the formation of hemoglobin following the administration of certain amino acids to rats fed a diet low in protein. They concluded that no single amino acid was of paramount importance in hemoglobin synthesis, but rather that a combination of amino acids

in unknown proportions was necessary for the elaboration of hemoglobin. The results of the present study tend to show that protein available as the hydrolysate by itself had no effect in enhancing the hemoglobin levels.

In view of these facts, it was thought worth while to compare the serum protein levels with the values for the hemoglobin and packed cell volumes. No statistical correlation could be found between the total protein values and either of the other two measurements but, when albumin levels were compared, the following positive correlations were found. When serum albumin levels and hemoglobin content of the blood (105 observations) were compared, a positive correlation of 0.57 with a standard error of ± 0.067 was found. The results for serum albumin levels and packed cell volume (105 observations) was 0.50 with a standard error of ± 0.073.

Each of these figures is significant and the difference between them is also significant. These figures clearly show that there is a relationship between the factors bearing on the level of serum albumin and the hemoglobin level, at any rate in those patients studied. A similar and lesser relationship is shown between the serum albumin level and the formation of red blood cells. The precise nature of these relationships is not clear, but it is tempting to speculate that the answer may be found in the synthesis of globin, at any rate so far as the synthesis of hemoglobin is concerned.

Total serum protein: The great majority of estimations fell within the normal limits chosen (6 to 8 Gm. per 100 ml.). This observation is of little value when the figures after fractionation are examined. Here it is apparent that in many cases a fall in serum albumin is accompanied by a rise in serum globulin as may be expected if the level of serum globulin is in part a measure of gamma globulin concentration and probably antibody formation. In fact, Kunkel (15) suggests that nearly every increase in serum globulin in states of hyperglobulinemia is due to an increase in the gamma globulin fraction of the serum. The relation of antibodies to this fraction of the serum is well known and lends itself to interesting speculation on the significance of altered globulin ratios in infectious diseases which are not primarily hepatic.

Serum albumin: At the beginning of the survey, 13 of the 38 patients had albumin levels of less than 3.6 Gm. per 100 ml., which was arbitrarily chosen as the lower limit of normal. The relation of the serum albumin values to hemoglobin level, the packed cell volume, and the blood sedimentation rate has already been discussed. The relation to the empiric liver function tests will be discussed later.

Serum globulin: Twenty, or approximately half, of the patients showed elevated serum globulin levels. This was an expected finding (*vide supra*).

Liver function tests: Three empiric liver function tests were carried out on every specimen of serum collected in order to attempt an estimate of the functional state of the liver. Of the three tests, cephalin cholesterol flocculation, serum colloidal gold test and the thymol turbidity test, only the last named showed any deviation from normal. In this test half the patients gave a reading of 5 or over. It is well known, however, that under certain conditions, if the

ionic strength of a solution is reduced, the solubility of certain proteins is reduced and they are precipitated. This principle is used to advantage in both the thymol turbidity test and the buffer dilution test of Wolff. The fact that the thymol turbidity test is probably associated with an excess of beta globulin in the serum, and also that certain lipemic sera show a marked increase in the beta globulin fraction, adds a complicating factor to the interpretation of the thymol turbidity test taken by itself as an indication of liver dysfunction.

Although clinical evidence of hepatic insufficiency is rare in tuberculosis, the more sensitive tests show that functional derangement is not uncommon. A series of patients examined by Kruger and Gerber (16) and Hurst *et al.* (17) showed abnormalities in a proportion of patients, predominantly in the very advanced phases of pulmonary tuberculosis. It is interesting to note that Hurst and his colleagues failed to show changes in hepatic function with both the oral and intravenous hippuric acid test.

The present results with the flocculation tests do not seem to confirm the finding of liver derangement in pulmonary tuberculosis. Only a small number of tests were carried out, however, and it is a well-known fact that functional ability of the liver cannot be measured by any single functional test; a veritable battery of tests measuring different functions seems to be the only safe measure. Maclagan (20), using the flocculation tests, found one positive test in 18 patients suffering from pulmonary tuberculosis. It is interesting to note also that significant deviations from the normal were only consistently obtained with the serial bromsulfalein test. If some of these empiric tests owe their positivity to the excess of gamma globulin in the serum, and good antibody response is likewise associated with an increased gamma globulin fraction of the serum, the interpretation of the increased gamma globulin fractions cannot be construed as evidence of liver disease in infectious diseases.

COMMENT

The original purpose of the present study was to demonstrate the effect, if any, of adding protein hydrolysate to the diet of adult colored males with tuberculosis. Clinical data were studied and, in addition, roentgenographic examinations of the chest, erythrocyte sedimentation rates, and the blood analyses outlined above were carried out in order to measure any change in clinical or nutritional state. The reasoning behind the experiment was that some tuberculous patients found difficulty in digesting first-class protein, such as meat. The idea of giving such patients protein hydrolysate is not a new one. The liver is intimately concerned in protein metabolism and probably synthesizes proteins from amino acids supplied to it from the blood. Thus it seems reasonable to assume that the liver could continue this function if furnished with the necessary amino acids provided its own function was not grossly deranged by a disease process. For this reason empiric liver function tests were carried out on all sera and, as already stated, revealed very little evidence of liver dysfunction by themselves. Cox and Mueller (18) found that orally or intravenously administereed protein hydrolysate was equally effective in the regeneration of plasma albumin in hypoproteinic patients.

TABLE 1

Determinations of Various Components of the Blood during Protein Hydrolysate Therapy

	TEST GROUP NO. OF PATIENTS			CONTROL GROUP NO. OF PATIENTS		
	Beginning	Third Week	Sixth Week	Beginning	Third Week	Sixth Week
Erythrocyte Sedimentation Rate; mm. in one hour.						
0 to 10 mm.	5	7	6	2	—	—
11 to 50 mm.	10	9	9	5	8	9
more than 50 mm.	4	3	4	12	11	7
Packed Cell Volume, per cent						
45 and above	13	14	13	7	9	9
35 to 44	6	5	6	11	8	7
less than 35	—	—	—	1	2	—
Hemoglobin Gm. per 100 ml.						
14 Gm. and above.	9	7	9	5	3	5
12 to 13.9 Gm.	8	11	9	5	6	6
less than 12 Gm.	2	1	1	9	10	5
Mean Corpuscular Hemoglobin Concentration, per cent						
32 and above	1	1	—	—	—	—
29 to 31	14	10	15	11	12	8
less than 29	4	8	4	8	7	8
Total Serum Protein Gm. per 100 ml.						
6 to 8 Gm.	17	19	19	16	17	13
more than 8 Gm.	2	—	—	2	2	2
less than 6 Gm.	—	—	—	1	—	—
Serum Albumin, Gm. per 100 ml.						
3.6 to 5 Gm.	16	16	18	9	13	10
less than 3.6 Gm.	3	3	1	10	5	5
Serum Globulin, Gm. per 100 ml.						
1.3 to 3.2 Gm.	12	12	11	6	3	6
3.3 to 5 Gm.	7	7	8	13	15	9
Thymol Turbidity Test (units)						
0 to 4	10	9	9	9	7	7
5 to 7	9	10	9	9	10	5
8 to 10	—	—	1	1	2	3
Colloidal Gold Test (units)						
0 to 2	17	18	18	17	16	13
3 to 5	2	1	1	2	3	2
Cephalin Cholesterol Flocculation Test						
0 to +	17	19	18	17	17	13
2^+ to 4^+	2	0	1	2	2	3

Madden and Whipple (19) showed that amino acids as the sole source of nitrogen in standardized dogs could produce plasma proteins and the response compared favorably with the response of first class proteins in corresponding amounts.

The precise values in the observations of the present study can be seen in table 1 and are set out in table 2 in detail. Each patient was studied separately and the change in this nutritional state recorded. The mean values were calculated as well as the Standard Deviation for the variance of the changes. The standard error of the mean was calculated from the formula $\frac{S.\ D.}{n-1.}$ where "n" is the number of patients studied.

All the values indicate a very slight increase (including the serum globulin values), but the second column shows clearly that all these figures can be disre-

TABLE 2

Change in Values after Six Weeks

	MEAN CHANGE	STANDARD ERROR OF THE MEAN
Total Serum Protein		
Test group	+0.21 Gm.	±0.17 Gm.
Control group	+0.09 Gm.	±0.14 Gm.
Serum Albumin		
Test group	+0.09 Gm.	±0.13 Gm.
Control group	+0.05 Gm.	±0.12 Gm.
Serum Globulin		
Test group	+0.04 Gm.	±0.18 Gm.
Control group	+0.20 Gm.	±0.19 Gm.
Packed Cell Volume		
Test group	+0.6 per cent	±0.89 per cent
Control group	+1.25 per cent	±0.61 per cent
Hemoglobin		
Test group	+0.02 Gm.	±0.31 Gm.
Control group	+0.08 Gm.	±0.25 Gm.

garded as being insignificant. The only possible exception is the mean increase in packed cell volume in the "control" group where the actual mean change was about twice its standard error. Such a result might occur by chance about once in twenty times. These data then fail entirely to show any measurable effect of the feeding of protein hydrolysates to these patients over a period of six weeks. The same conclusion was reached after intensive and careful study of the clinical and radiological records.

SUMMARY

Thirty-eight patients with pulmonary tuberculosis were divided into two equal groups. One group received an additional dietary supplement of 50 Gm. of protein hydrolysate per day.

The results of this treatment were gauged by clinical, roentgenographic, and biochemical methods.

During the six weeks period of observation no beneficial effects of statistical significance were noted which could be attributed to the increased protein in the diet.

SUMARIO

Hidrolisato de Proteína por Vía Oral en la Tuberculosis Pulmonar

Treinta y ocho tuberculosos pulmonares fueron divididos en dos grupos iguales, recibiendo un grupo, como complemento dietético, 50 Gm. diarios de hidrolisato de proteína.

El resultado de este tratamiento fué justipreciado clínica, radiográfica y bioquímicamente.

Durante el período de observación de seis semanas no se observaron efectos beneficiosos de cuantía estadística que pudieran imputarse al aumento de proteína en la alimentación.

Acknowledgment

We wish to thank Prof. R. Turner for permission to publish this paper. We are indebted to Dr. J. F. Wicht, Medical Superintendent of Hospitals, for advice and interest. To Dr. F. Ames we are grateful for excellent supervision of the patients and collection of the blood samples.

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SUPPLEMENTARY ORAL PROTEIN HYDROLYSATE THERAPY IN TUBERCULOSIS[1]

SAMUEL COHEN AND Y. Y. MA

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INTRODUCTION

The importance of adequate protein nutrition in a number of medical and surgical conditions has been frequently stressed in recent years. Protein deficiency may be due to an insufficient intake, poor absorption or assimilation, excessive protein destruction or loss. In infection, the degree and duration of destruction of protein depends on the severity and chronicity of the disease. The attempt to utilize protein for repair of damaged tissue takes precedence over and may occur at the expense of the catabolism of normal tissue. Consequently, it is probable that the ordinary hospital diet may not at times be adequate to supply this combined demand for protein. Also, a higher than usual caloric intake may be necessary because, if fats and carbohydrates are not present in sufficient amount, protein will be burned for heat. The quality of protein as well as its quantity is important too. Animal protein is generally preferable to vegetable protein. A deficiency of protein may be due to an insufficiency of protein per se or of specific amino acids. Of the twenty-one amino acids, eight are considered as essential in man for the formation of protein and other nitrogenous compounds. These essential amino acids cannot be synthesized by the body but must be supplied in the food.

An experiment was undertaken in a group of patients with far advanced tuberculosis to supplement the regular hospital dietary with the oral use of amino acid mixtures available in protein hydrolysates. An attempt was made to correlate the value of this nutritional regimen with clinical observations and laboratory determinations.

MATERIALS AND METHODS

Selection of patients: Patients were selected who fulfilled the following criteria: (*1*) residence in hospital for at least six months prior to the supplementary use of protein hydrolysates; (*2*) evidence of unfavorable clinical and/or roentgenological course with sputum positive for *M. tuberculosis*, weight loss, and fever. Attempts at collapse therapy had been unsuccessful in these patients or they were considered unsuitable for such therapy when the study was begun.

During the preliminary observation period, the patients received a general diet which in this hospital ranges from 2,500 to 2,700 calories with an average protein allowance of 70 to 90 Gm. In addition, the patients received between meal nourishment of three glasses of milk daily or an approximate equivalent substitute depending on the patients' preference, and also a supplementary intake of vitamins.

Clinical and laboratory studies: A physical examination was done at the onset and repeated as indicated. Sputum examinations were ordered as necessary. Roentgenograms of the chest were taken before therapy and at approximately three month intervals. The

[1] From the Berthold S. Pollak Hospital for Chest Diseases, Medical Center, Jersey City, New Jersey.

maximum and standard normal (for corresponding age, sex, height) weight records were noted on admission and at weekly intervals thereafter. The additional laboratory determinations which were made prior to and at one to three month intervals during therapy included: (1) hematocrit (Haden method); (2) erythrocyte sedimentation rate (Cutler method); (3) concentration of serum protein and the albumin globulin ratio (Reiner method); (4) blood volume with T-1824 dye (Gibson and Evans method (1), modified by Nobile *et al.*, (2)); and (5) the plasma volume and the total circulating protein which were calculated from the above determinations.

Protein hydrolysate products: Three preparations were employed: (*1*) Protolysate, a dry enzymic digest of casein containing amino acids and polypeptides; (*2*) Edamin, a tryptic hydrolysate of milk protein which consisted primarily of amino acids and peptides derived from lactalbumin; (*3*) Granules-Protein-Mineral Mixture, a protein of liver origin subjected to partial digestion with added minerals. The respective total nitrogen percentage content of each preparation was 12.0, 12.0, 7.0.

Method of hyperalimentation therapy: The daily hydrolysate intake for each patient was calculated according to the following formula. The total daily nitrogen requirement based on the patient's observed weight was computed on the arbitrary basis of 0.6 Gm. per Kg. and the known nitrogen content of the proprietary product used. The total caloric intake was estimated using 40 calories per Kg. as the standard. Since one gram of protein hydrolysate yields 4 calories, the protein caloric intake was available. To make up the deficit in the total calories, Dextri-Maltose #2 (without salt) was employed. It is palatable and acts as a protein sparer or protector of body protein, relieving tissue protein of the necessity of furnishing energy. For example, a patient weighing 60 Kg. will need 36 Gm. of nitrogen daily. Assuming that protolysate is used, 12 Gm. of nitrogen are furnished by 100 Gm. of this product, so that a total of 300 Gm. is necessary. This furnishes 1,200 calories. The total caloric requirement of this 60 Kg. individual is 2,400. Therefore, the caloric deficit (2,400 minus 1,200) is 1,200 which is furnished by the 300 Gm. of Dextri-Maltose #2.

In the preparation of the mixture, the latter was first dissolved in one or one and one-half liters of boiled water to which the specific protein hydrolysate product was then added. The mixture was prepared fresh daily and kept in a refrigerator. Four or five divided oral feedings were given before or after meals according to the patients' preference. In addition, each patient received a diet of about 2,500 calories, containing 75 Gm. of protein.

RESULTS

A total of 9 patients with far advanced tuberculosis were placed on the hyperalimentation diet. Three died from their basic disease very soon after therapy was begun and should properly be excluded for any fair evaluation of this mode of therapy. Six patients were maintained on the hyperalimentation regimen over a period ranging from approximately six to eleven months. Four of the surviving patients were then placed on the routine hospital diet and final observations were recorded six months later. A control period was therefore available before and after hyperalimentation was instituted. A summary of the pertinent observations in each of the 6 cases is presented.

CASE REPORTS

Case I: F. L., a 36 year old white male (figure 1) was known to have had pulmonary tuberculosis since 1930. In 1933 he had a two stage thoracoplasty which was ineffective. His last hospital admission occurred in May, 1943 because of increased pulmonary symptoms and a loss of 20 lbs. in five months. The patient's weight on admission was 126.5 lbs. and on a regimen of bed rest (further surgical therapy was contraindicated) and the ordinary

hospital diet, his weight had declined to 102 lbs. on July 1, 1946. The temperature ranged up to 100°F. On September 16, amino acid therapy (Edamin and Dextri-Maltose 240 Gm. each) supplementing a regular diet containing 75 Gm. of protein was initiated. The weight was now 104 lbs., the sputum was positive for tubercle bacilli and a chest roentgenogram,

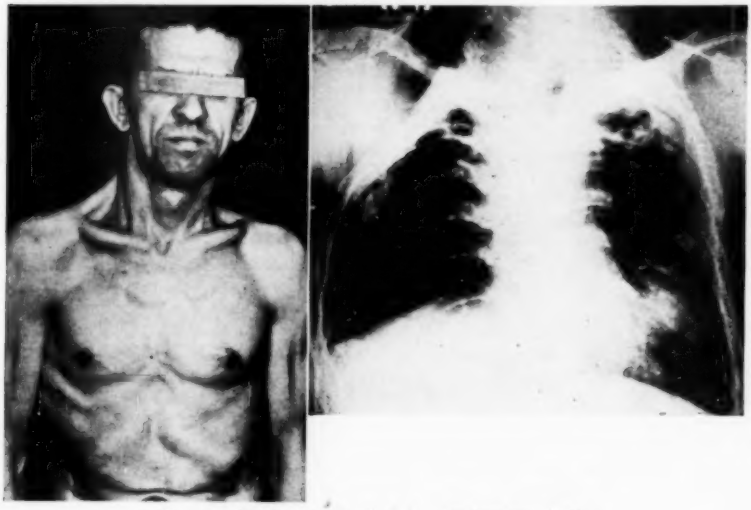

FIG. 1. (Left) Case I (F. L.). September, 1946
FIG. 2. (Right) Case I. September 10, 1946

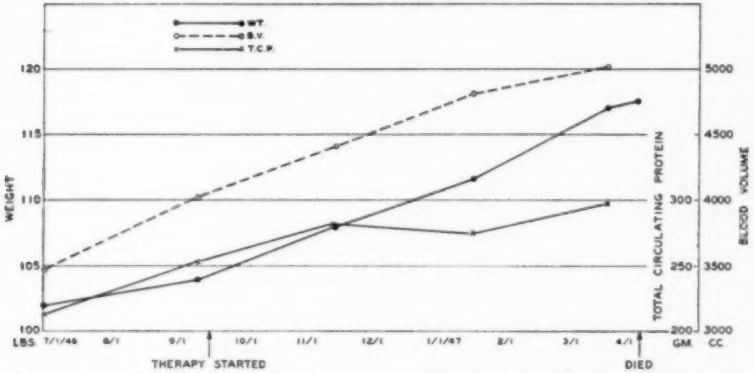

FIG. 3. Case I. Relation of blood volume, weight and total circulating protein

September 10, 1946, (figure 2) revealed evidence of a right sided thoracoplasty, bilateral productive disease with cavitation, a recent bronchopneumonic spread on the left, and adhesive pleurisy. The patient exhibited no significant untoward gastro-intestinal symptoms during the period of dietary therapy. He made no serious objection to the taste of the amino acid preparation.

The patient had recurrent small hemoptyses from October, 1946 through March, 1947. A roentgenogram of the chest in November, 1946 showed some resolution of the exudative process on the left. No significant change was observed in a film taken in February, 1947. On April 3, 1947, the patient suddenly developed dyspnea, rapid pulse, and died. A post-

TABLE 1

Summary of Data, Case I (F. L.)

DIET	DATE	WEIGHT	E.S.R.	HEMATOCRIT	SERUM PROTEINS	PLASMA VOLUME	BLOOD VOLUME	TOTAL CIRCULATING PROTEINS
		lbs.			*Gm.*	*cc.*	*cc.*	*Gm.*
	5/11/43 (Admitted)	126.5	—	—	—	—	—	—
Regular	7/ 1/46	102	26	24	T.P.—7.1 A.—4.5 G.—2.6 A/G—1.7:1	2,999	3,496	213
	9/10/46	104	26	22	T.P.—8.7 A.—4.9 G.—3.8 A/G—1.3:1	3,125	4,006	253
Regular plus oral amino acid therapy Edamin—240 Gm. D.M.—240 Gm. Started 9/16/46	11/14/46	108	28	23	T.P.—8.1 A.—4.0 G.—4.1 A/G—0.97:1	3,423	4,419	280
	1/16/47	111.5	24	24	T.P.—7.5 A.—4.5 G.—3.0 A/G—1.5:1	3,660	4,810	275
	3/18/47	117	26	24	T.P.—7.8 A.—4.8 G.—3.0 A/G—1.6:1	3,813	5,017	297
	4/ 2/47	117.5 Last recorded weight	—	—	—	—	—	—
	4/ 3/47 (died)							

mortem film revealed a considerable density on the left indicative of probable atelectasis of the left lung.

Prior to death, the patient showed gratifying constitutional improvement for which the new dietary regimen could receive much or all of the credit. His last recorded weight on

April 2, 1947 was 117.5 lbs. which represented a gain of 13.5 lbs. during the more than six plus months of supplemental amino acid therapy. The increase in the weight was paralleled by an increase in blood volume and a slightly less marked increase in the total circulating protein. The hematocrit determinations were consistently subnormal and significantly

TABLE 2

Summary of Data, Case II (R. T.)

DIET	DATE	WEIGHT	E S.R.	HEMATOCRIT	SERUM PROTEINS	PLASMA VOLUME	BLOOD VOLUME	TOTAL CIRCULATING PROTEINS
		lbs.			*Gm.*	*cc.*	*cc.*	*Gm.*
	1/ 7/46 (Admitted)	123	—	—	—	—	—	—
	Apr./46 (max.)	143	—	—	—	—	—	—
Regular	7/ 1/46	129.5	28	22	T.P.—7.5 A.—4.7 G.—2.8 A/G.—1.6:1	3,390	4,346	254
	9/10/46	121	26	21	T.P.—7.9 A.—4.9 G.—3.0 A/G.—1.6:1	3,129	3,960	247
Regular plus oral amino acid therapy Edamin—275 Gm. D.M.—275 Gm. Started 9/16/46 Protein Granules (200 Gm.) Substituted 12/20/46	11/14/46	116	24	21	T.P.—7.5 A.—4.1 G.—3.4 A/G.—1.2:1	3,662	4,637	274
	1/16/47	108	29	20	T.P.—7.2 A.—3.6 G.—3.6 A/G.—1:1	3,280	4,100	236
	2/ 5/47	105 Last weight record	—	—	—	—	—	—
	3/ 8/47 (died)	—	—	—	—	—	—	—

unchanged. The total serum protein concentrations remained within normal limits although the albumin-globulin ratio was depressed (table 1, figure 3).

Case II: R. T., a white male, age 43 (figure 4), was admitted January 7, 1946 with bilateral far advanced infiltrative and cavernous tuberculosis with sputum positive for tubercle bacilli. On bed rest his weight increased from 123 lbs. on admission to a maximum of 143 lbs. in April, 1946. A chest roentgenogram in September, 1946 (figure 5) showed dis-

seminated bilateral disease with multiple cavities and diaphragmatic pleurisy. The sputum remained positive for *M. tuberculosis* and the average daily febrile peak was 101°F. On September 16, 1946, a 75 Gm. protein diet was supplemented with Edamin and Dextri-Maltose, 275 Gm. each. The patient's weight was then 121 lbs. He experienced frequent

FIG. 4. (Left) Case II (R. T.). September, 1946
FIG. 5. (Right) Case II. September, 1946

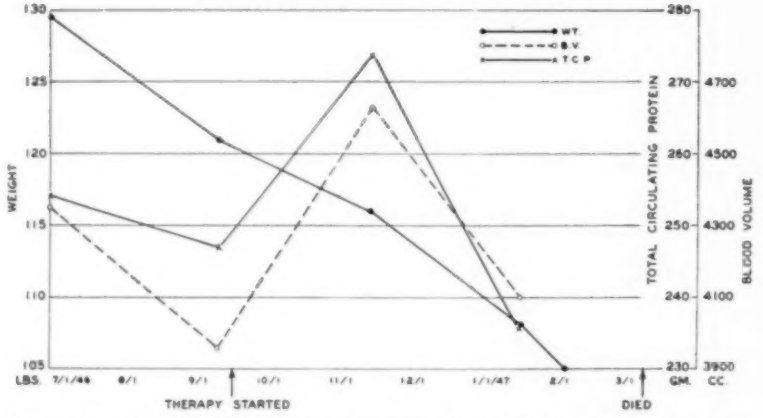

FIG. 6. Case II. Relation of blood volume, weight and total circulating protein

nausea, vomiting, abdominal cramps and occasional diarrhea. On December 20, 1946 Protein Granules (200 Gm.) was substituted with some abatement of symptoms. However, amino acid therapy had to be reduced in quantity or discontinued for short intervals. The patient frequently could not ingest all of his regular diet either. He gradually became

weaker, lost weight and his disease progressed, as determined on subsequent roentgenograms. The patient died March 9, 1947 after a therapy period of approximately six months.

TABLE 3

Summary of Data. Case III (P. D.)

DIET	DATE	WT.	E.S.R.	HEMATOCRIT	SERUM PROTEINS	PLASMA VOLUME	BLOOD VOLUME	TOTAL CIRCULATING PROTEINS	LIVER FUNCTION TESTS
		lbs.			*gm.*	*cc.*	*cc.*	*gm.*	
	1/25/43 (Admitted)	Not recorded	—	—	—	—	—	—	
	Aug./43	136	—	—	—	—	—	—	
Regular	9/24/46	142.5	25	24	T.P. —7.7 A —4.5 G —3.2 A/G.—1.3:1	3,526	4,640	271	
	10/24/46	138.5	24	24	T.P. —7.5 A —5.3 G —2.2 A/G.—2.4:1	3,231	4,251	245	
	1/23/47	136.5	23	24	T.P. —7.8 A —5.4 G —2.4 A/G.—2.2:1	2,816	3,657	219	Bromsulfalein dye test 1/30/47—6.5 per cent retention 12/18/47—Negative
Regular plus oral amino acid therapy Protolysate—310 Gm. D.M.—310 Gm. Started 10/28/46	4/23/47	145.5	22	22	T.P. —7.4 A —4.9 G —2.5 A/G.—1.9:1	3,521	4,512	260	
	7/8/47	148	25	21	T.P. —8.2 A —4.6 G —3.6 A/G.—1.2:1	3,817	4,831	312	Cephalin Flocculation 1/30/47—Negative 12/18/47—Negative
	9/16/47	152.5	23	24	T.P. —8.2 A —5.4 G —2.8 A/G.—1.9:1	4,453	5,859	345	
Regular from 9/17/47 to 3/10/48	12/16/47	151	23	25	T.P. —6.8 A —4.4 G —2.4 A/G.—1.8:1	3,650	4,866	248	
	3/10/48	140.5	23	22	T.P. —6.1 A —3.8 G —2.3 A/G.—1.6:1	3,497	4,483	214	

The dietary program was definitely unsatisfactory but his prognosis was hopeless from the beginning. There was poor correlation between the blood volume and weight records. The hematocrit was low, the serum protein concentration normal, but the albumin-globulin ratio was subnormal (table 2, figure 6).

Case III: P. D., a 43 year old white male (figure 7) was admitted February 25, 1943 with a history of pulmonary tuberculosis since January, 1942. On admission, the patient had hemoptyses, bilateral productive and cavernous disease, and sputum positive for *M. tuber-*

FIG. 7. (Left) Case III (P. D.). October, 1946
FIG. 8. (Right) Case III. October 4, 1946

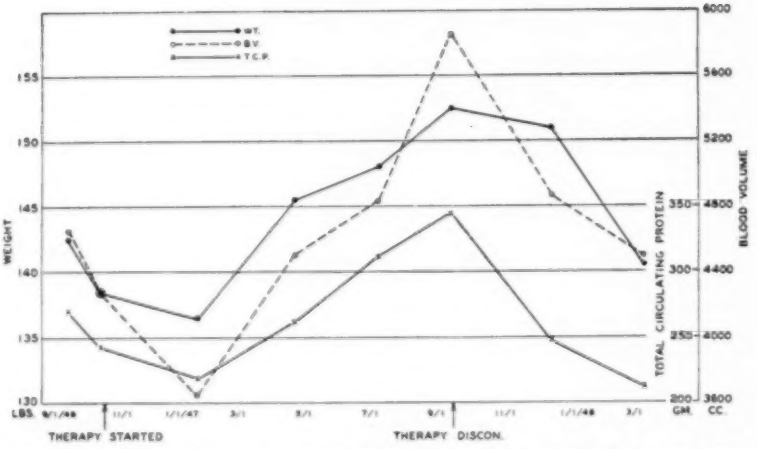

FIG. 9. Case III. Relation of blood volume, weight and total circulating protein

culosis. His standard normal weight was 160 lbs., the maximum 195 and the entrance weight was not recorded because of the pulmonary bleeding. In August, 1943 his weight was 136 lbs. and during the next three years he gained up to 142.5 lbs. (September 24, 1946), although his weight dropped to 138.5 lbs. one month later. A roentgenogram of the chest

(October 10, 1946) (figure 8) revealed that considerable clearing had occurred compared to the admission findings but residual bilateral emphysema with productive infiltration and multiple small cavities persisted in the upper lung fields. The sputum was positive for *M. tuberculosis* and he had the additional complications of amyloidosis (albuminuria, enlarged liver, 100 per cent retention of congo red in tissue) and hoarseness without dysphagia.

On October 28, 1946, the hyperalimentation regimen was begun consisting of the 75 Gm. protein diet plus Protolysate (310 Gm.) and an equal amount of Dextri-Maltose. During the first two months, the patient vomited about once every other day and had diarrhea for one day. His weight declined to 136.5 lbs. in January, 1947, but thereafter showed a steady increase to 152.5 lbs. on September 16, 1947, when the dietary therapy was discontinued after a period of approximately eleven months. In other words, his 14 lb. net gain in weight (from 138.5 to 152.5) in this latter interval was greater than had occurred in the three year previous period while on the ordinary hospital diet. No very significant change in the pulmonary process was noted on serial roentgenograms. The sputum remained positive for *M. tuberculosis*, albuminuria diminished, hoarseness persisted and another congo red test (October 3, 1947) showed no change. During supplemental amino acid therapy, there was a concomitant and significant increase in the plasma and blood volumes and the circulating protein; the serum protein and the albumin-globulin ratio remained essentially normal (table 3, figure 9). An abnormal value for the bromsulfalein test, which was noted about three months after treatment was started, became normal on completion of the dietary therapy.

The patient reverted to the original regular diet alone and observations were made in this control period during the six month interval between September, 1947 and March, 1948. He maintained almost the same weight for about three months and then a decline occurred to 140.5 lbs. The plasma and blood volumes and the circulating blood protein also diminished and the albuminuria increased (qualitative determination). Fluoroscopic and roentgenographic examinations of the chest in this period revealed no change.

The evidence strongly indicates that the addition and subsequent subtraction of the protein hydrolysate from the regular diet in this patient was directly related to the rise and fall in weight.

Case IV: J. M., a 41 year old white male (figure 10), entered the hospital April 10, 1941 with bilateral pulmonary tuberculosis and a large cavity in the left upper lobe. His weight was 110 lbs. and the highest recorded weight was 112 lbs. on May 28, 1946. A two stage thoracoplasty (left) was done September, 1946. Further operation was contraindicated because of poor respiratory reserve and a residual cavity and sputum positive for *M. tuberculosis* persisted (figure 11). Following thoracoplasty, the weight declined and on December 20, 1946 it was 99 lbs. at which time he was started on the diet containing 75 Gm. of protein and supplemented by Protolysate and Dextri-Maltose, 225 Gm. each. The patient's objection to the taste of the product was overcome by the addition of 4 cc. of peppermint water to the liter of mixture. He vomited once on the first day but at no time did he have abdominal cramps or diarrhea. Hyperalimentation therapy was stopped in September, 1947 after about nine months. At this time his weight was 107.5 lbs. which represented a gain of 8.5 lbs. The plasma and blood volumes and the circulating protein determinations fluctuated and showed no consistent correlation with the weight records (table 4, figure 12). Two liver function tests were normal.

During the second control period of six months with resumption of the regular hospital diet, the patient exceeded slightly the last recorded weight while he received Protolysate (107.5 to 109.5 lbs.). Serial roentgenograms showed some diminution in size of the residual cavity (left) both during amino acid therapy and subsequently, but the improvement was attributed to the bed rest regimen.

In summary, this patient tolerated well the hyperalimentation diet which was begun approximately three months after the thoracoplasty operation because of

TABLE 4

Summary of Data, Case IV (J. M.)

DIET	DATE	WT.	E.S.R.	HEMATOCRIT	SERUM PROTEINS	PLASMA VOLUME	BLOOD VOLUME	TOTAL CIRCULATING PROTEINS	LIVER FUNCTION TESTS
		lbs.			*gm.*	*cc.*	*cc.*	*gm.*	
	Apr./41	110 (admitted)	—	—	—	—	—	—	
Regular	11/19/46	97	26	22	T.P. —7.7 A —5.7 G —2.0 A/G.—2.8:1	2,077	2,663	159	
	12/19/46	99	21	26	T.P. —6.6 A —4.3 G —2.3 A/G.—1.8:1	1,982	2,678	130	
	2/19/47	100.5	19	24	T.P. —6.5 A —4.0 G —2.5 A/G.—1.6:1	2,412	3,173	156	Bromsulfalein dye test 1/30/47—1.0 per cent retention 12/23/47—0.5 per cent retention
Regular plus oral amino acid therapy	4/24/47	101	11	29	T.P. —7.9 A —4.9 G —3.0 A/G.—2.6:1	1,832	2,410	144	
Protolysate—225 Gm. D.M.—225 Gm. Started 12/20/46	7/8/47	102.5	20	22	T.P. —8.3 A —5.7 G —2.6 A/G.—2.2:1	2,040	2,615	217	Cephalin Flocculation 1/30/47—Negative 12/23/47—Negative
	9/14/47	107.5	19	23.5	T.P. —8.2 A —5.0 G —3.2 A/G.—1.5:1	1,723	2,252	141	
Regular (from 9/15/47 to 3/10/48)	12/16/47	109.5	15	27	T.P. —7.3 A —4.7 G —2.6 A/G.—1.8:1	2,139	2,930	156	
	3/10/48	109.5	16	23	T.P. —6.3 A —3.9 G —2.4 A/G.—1.2:1	2,366	3,072	149	

his slow constitutional recovery. An increase in weight followed and this tendency was maintained after amino acid therapy was stopped.

Case V: I. F., a 35 year old white female (figure 13) with a history of tuberculosis since 1937

and an unsuccessful period of bilateral artificial pneumothorax therapy, entered the hospital February 18, 1946. The sputum was positive for *M. tuberculosis* and the admission

FIG. 10. (Left) Case IV (J. M.). December, 1946
FIG. 11. (Right) Case IV. November 4, 1946

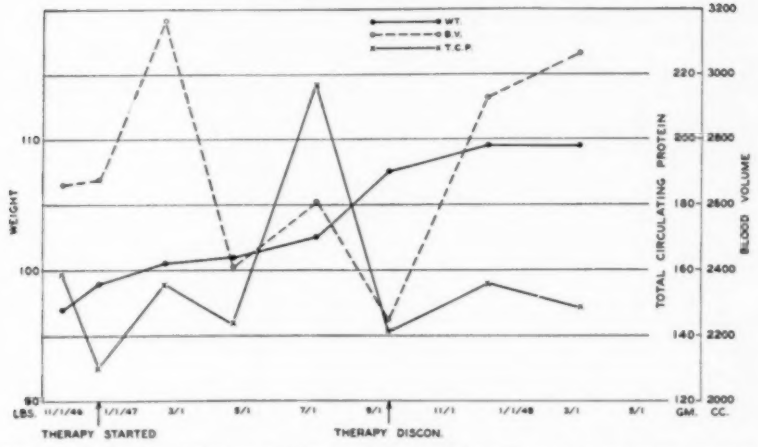

FIG. 12. Case IV. Relation of blood volume, weight and total circulating protein

film of the chest revealed bilateral disseminated infiltration with cavitation. The patient had an intermittent low grade fever. On bed rest, she gained from 101 lbs. on admission to a maximum of 116 lbs. in August, 1946, but the weight then dropped gradually to 105 lbs. in March, 1947. A chest roentgenogram (figure 14) showed in comparison to the admission

status slight resolution of the infiltrate in some areas but a definite increase in size of cavitation.

Hyperalimentation therapy was started March 21, 1947 with the addition to the usual diet of 240 Gm. each of Edamin and Dextri-Maltose. Occasional nausea and vomiting

TABLE 5

Summary of Data, Case V (I. F.)

DIET	DATE	WT.	E.S.R.	HEMATOCRIT	SERUM PROTEINS	PLASMA VOLUME	BLOOD VOLUME	TOTAL CIRCULATING PROTEINS	LIVER FUNCTION TESTS
		lbs.			*gm.*	*cc.*	*cc.*	*gm.*	
	2/18/46	101 (admitted)	—	—	—	—	—	—	
	Aug./46	116 (max.)	—	—	—	—	—	—	
Regular	3/20/47	105	25	21.5	T.P. —5.8 A —3.2 G —2.6 A/G.—1.2:1	2,851	3,621	165	
	4/24/47	104	27	20	T.P. —7.4 A —4.6 G —2.8 A/G.—1.3:1	2,355	2,945	174	Bromsulfalein dye test 3/23/47—8.5 per cent retention 12/29/47—Negative
Regular plus amino acid therapy Edamin—240 Gm. D.M.—240 Gm. Started 3/21/47	5/22/47	101.5	27	19	T.P. —8.1 A —4.5 G —3.6 A/G.—1.3:1	2,233	2,757	180	
Protein granules —350 Gm. D.M.—350 Gm. Started 5/12/47	7/24/47	98	26	19.5	T.P. —8.4 A —5.7 G —2.7 A/G.—2.1	2,438	2,931	204	Cephalin Flocculation 3/23/47 + 12/29/47—Negative
	9/9/47	97	19	20	T.P. —8.1 A —4.7 G —3.4 A/G.—1.3:1	2,238	2,797	181	
Regular (from 9/10/47 to 3/12/48)	12/18/47	94.5	24	24	T.P. —7.8 A —4.6 G —3.2 A/G.—1.4:1	2,046	2,692	159	
	3/12/48	90	22	18	T.P. —7.0 A —4.1 G —2.9 A/G.—1.4:1	2,347	2,862	164	

occurred and, because the mixture became distasteful, 350 Gm. of Protein Granules were substituted on May 12, 1947. This product was more palatable but had to be discontinued on occasions. After approximately six months, the dietary regimen was stopped in September 1947. Progression of the pulmonary disease on the right side was noted and she lost 7 lbs. (from 104 to 97) during therapy. Further loss of weight occurred in the six months post-therapy observation period, 90 lbs. on March 12, 1948, although the roentgenogram of the chest showed slight regression of disease.

The blood volume and the circulating protein determinations for the most part did not parallel the weight records (table 5, figure 15). The result of the bromsulfalein test was definitely abnormal at the onset of treatment and later reverted to normal.

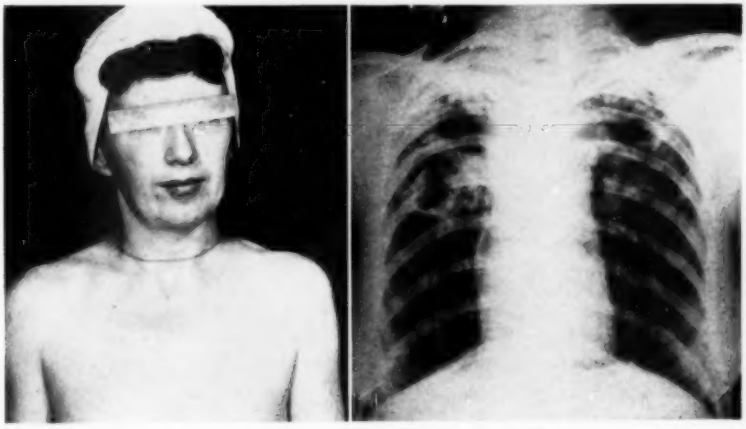

FIG. 13. (Left) Case V (I. F.). March, 1947
FIG. 14. (Right) Case V. March 3, 1947

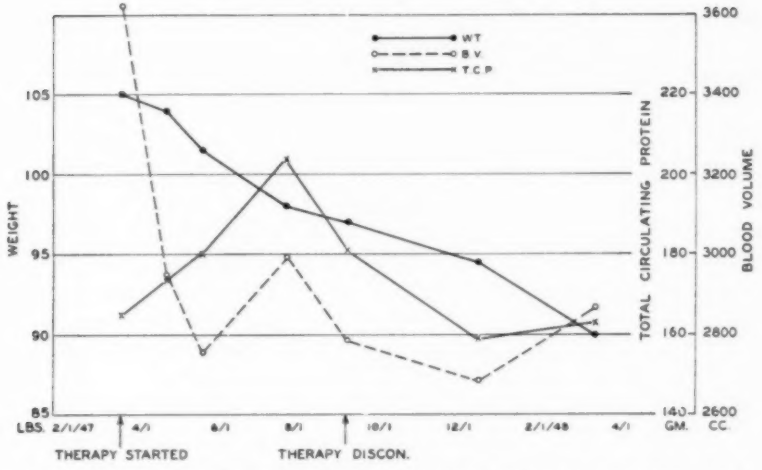

FIG. 15. Case V. Relation of blood volume, weight and total circulating protein

In summary, the results with hyperalimentation in this patient were poor both from the point of view of tolerance to it and from other objective findings. The unfavorable constitutional trend which was present before and during treatment also continued after its cessation.

Case VI: J. D., a 22 year old white male (figure 16) was readmitted November 18, 1946. The patient was febrile, in poor general condition, the sputum was positive for *M. tuberculosis* and a chest roentgenogram revealed a large upper lobe cavity (left) with bronchopneumonic disease and minimal infiltration (right). Artificial pneumothorax was induced but later discontinued. His weight on admission was 110 lbs., reached a peak of 115 lbs. in January,

TABLE 6

Summary of Data, Case VI (J. D.)

DIET	DATE	WT.	E.S.R.	HEMATOCRIT	SERUM PROTEINS	PLASMA VOLUME	BLOOD VOLUME	TOTAL CIRCULATING PROTEINS	LIVER FUNCTION TESTS
		lbs.			*gm.*	*cc.*	*cc.*	*gm.*	
Regular	11/18/46	110 (admitted)	—	—	—	—	—	—	
	1/13/47	115 (max.)	—	—	—	—	—	—	
	3/20/47	103	36	23	T.P. —7.7 A —4.0 G —3.7 A/G.—1.09:1	3,264	4,239	251	
Regular plus Protein Granules —405 Gm. DM—405 Gm. Started 3/21/47	4/23/47	102	25	19	T.P. —7.2 A —5.2 G —2.0 A/G.—2.6:1	2,323	2,868	168	Bromsulfalein dye test 3/30/47—13 per cent Retention 12/29/47—1 per cent Retention
	5/22/47	100	26	18.5	T.P. —7.4 A —5.3 G —2.1 A/G.—2.5:1	2,500	3,205	185	
	7/24/47	98	24	22	T.P. —8.0 A —5.4 G —2.6 A/G.—2.1	2,324	2,980	186	Cephalin Flocculation 3/30/47 ++ 12/29/47 0
	9/ 9/47	97	19	24	T.P. —7.8 A —4.9 G —2.9 A/G.—1.6:1	2,256	2,968	176	
Regular (9/10/47-3/12/48)	12/14/47	93	20	22.5	T.P. —6.5 A —4.4 G —2.1 A/G.—2:1	2,042	2,634	132	
	3/12/48	108.5	23	22	T.P. —7.4 A —5.3 G —2.1 A/G.—2.4:1	2,436	3,123	180	

1947 and then declined to 103 lbs. on March 21, when the hyperalimentation diet was initiated. The patient received 450 Gm. of the Protein-Granules-Mixture plus an equivalent amount of Dextri-Maltose and the associated regular diet. A roentgenogram of April 15, 1947 (figure 17) was used to visualize the status of the re-expanded left lung with its large cavity and fluid level. Occasional low grade fever was present.

It was hoped that the new diet might contribute toward sufficient improvement so that

surgical collapse therapy could be undertaken. Because a chest film in May, 1947 revealed more disease in the right lung, streptomycin therapy was started, and continued for six months. The patient lost 5 lbs. but roentgenologic improvement of the lesion occurred

FIG. 16. (Left) Case VI (J. D.). March, 1947
FIG. 17. (Right) Case VI. April 15, 1947

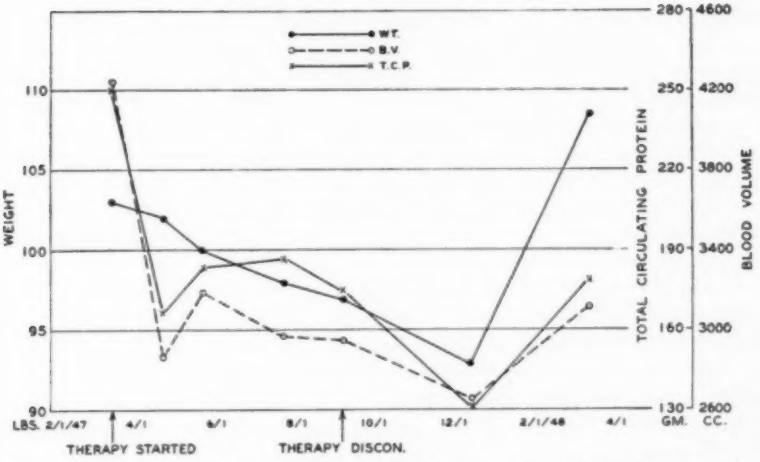

FIG. 18. Case VI. Relation of blood volume, weight and total circulating protein

and a three stage thoracoplasty was done under local anaesthesia. The first operation was performed in September, 1947, when the hyperalimentation program ended after nearly six months. The third stage was completed November 24, 1947. The patient tolerated the

surgical procedures very well. Following operation he slowly gained weight (11.5 lbs.) up to 108.5 lbs. on March 12, 1948 when the control period with the reinstituted regular diet terminated. Reference to table 6 and figure 18 indicates that the blood volume and total circulating protein followed in rather close parallel direction with the recorded weights.

In brief, it is seen that a loss of weight occurred with the hyperalimentation regimen and this trend was reversed after thoracoplasty when the regular diet was resumed.

COMMENT

The value of maintaining an optimum nutritional standard, aside from an adequate vitamin and mineral intake, in the treatment of a chronic disease, such as pulmonary tuberculosis, needs no defense. Unquestionably sufficient calories must be available to supply energy for basal needs and for tissue repair. While calories can be furnished by many foods, protein is an essential constituent of tissue which cannot be replaced by other foodstuffs. Furthermore, the storage of protein in the body is limited and must be constantly replenished in contrast, for example, to the body store of food in the form of adipose tissue.

The conventional quota of one Gm. of protein per Kg. body weight may suffice for the diet of the average individual but in patients with loss of weight, wasting of muscle, proteinuria, serous cavity exudates, et cetera, the allowance of protein must be increased. Lund and Levenson (3) and Elman (4) among many others have emphasized the manifestations of protein deprivation and its importance in relation to shock, susceptibility to infection, wound healing, nutritional edema, and in the hepatic detoxication of various toxins.

However, protein in the form in which it is ingested cannot be incorporated in the tissues. It must first be converted into amino acids which in turn become the basic constituents for the formation of the complex proteins of the cells and plasma proteins. This synthesis takes place primarily in the liver. It is possible that in some instances of tuberculosis a damaged liver may not carry out the normal function of manufacturing the proteins that it ordinarily furnishes to the body and which in turn protect it against further injury. It is interesting to note in 3 patients of the present series, that restoration to normal of an abnormal retention of the bromsulfalein dye followed the hyperalimentation regimen. It would be difficult to state, however, that these results by themselves may be used as an index of improvement in the protein metabolism of the liver.

The study of diet with the amino acids as tools has been projected in recent years for the correction of protein deficiency. Cannon (5) has postulated that for "tissue synthesis all the essential amino acids must be available in adequate amounts and proportions one to another and at approximately the same time." The employment of protein hydrolysates (by oral, tube feedings, or parenteral administration) as substitutes or supplements to the diet has become the vogue in the treatment of some medical and surgical conditions. Co Tui (6) commented on the oral use of a protein hydrolysate with Dextri-Maltose in 3 cases of advanced tuberculosis treated on the Chest Service of Bellevue Hospital. All showed an increase in weight and regression of disease and the latter became ap-

parent after five to seven months of therapy. It was felt that these patients revealed more improvement with the combination of bed rest and hyperalimentation than could have been expected ordinarily. In none, however, was there an increase in the plasma protein to match the increase in weight.

Many patients with advanced disease will show significant constitutional and roentgenologic improvement for variable periods of time with bed rest and the usual dietary program. In this report, the clinical proctocols of the patients, together with their photographs and chest roentgenograms at the time the hyperalimentation commenced, give adequate visualization of their generally poor condition and the far advanced tuberculosis. It is believed that the control periods of the experiment in these 6 cases in comparison with results obtained during the dietary therapy permitted a fair evaluation of hyperalimentation. Three patients (Cases I, III, IV) showed significant constitutional response with gain in weight for which the supplemental protein hydrolysate regimen deserves most or all of the credit. The pulmonary lesion was improved in 2 and stationary in one but these effects could not be properly attributed to hyperalimentation per se. One patient (Case I) died suddenly and 2 are living after the regular diet was resumed. One of these patients (Case III) lost weight and the other (Case IV) continued to increase his weight. The second group of 3 patients (Cases II, V, VI) lost weight during hyperalimentation and also revealed roentgenologic progression of tuberculosis, although in one the disease subsequently became quiescent probably due to streptomycin therapy, and thoracoplasy was performed. This patient (Case VI) thereafter gained weight on the regular diet alone. Another living patient (Case V) continued to lose weight after the ordinary hospital diet was reinstituted, while Case II died from further dissemination of pulmonary tuberculosis.

The laboratory test which has been used most widely in the detection of protein deficiency is the concentration of the plasma or serum protein. According to Peters and Eisenman (7) the normal range of total protein is from 6.0 to 8.0 Gm. per 100 cc.; the albumin is between 4.0 and 5.5 and the globulin from 1.4 to 3.0 Gm per 100 cc. This test, however, does not necessarily afford an index to the protein store in the body, as in patients with a slow development of protein malnutrition there may be no manifest hypoproteinemia until a considerable protein deficiency occurs in the tissues. Also in protracted infections there is frequently a shrinkage of the blood volume with loss of water which results in a relative increase in the serum protein (8). The actual concentrations of the albumin and globulin fractions are of more significance than their ratio. A lowered albumin, especially below 2.5 Gm. per 100 cc., is usually associated with frank edema although such factors as bed rest and dehydration may retard or lessen the edema. None of the patients actually showed edema or hypoproteinemia below the critical level; the globulin on occasions was high normal or above. Determinations of the plasma and blood volumes and the total circulating blood protein may give a more accurate picture of the state of protein nutrition, particularly in the earlier stages of deficiency and before the onset of edema. Chow (9) has stated that regeneration of total protein may occur after the administra-

tion of protein hydrolysate, even with a decrease of plasma protein concentration, because of a larger increase in plasma volume. In the present dietary study, the changes in the serial determinations of the circulating protein generally, though not invariably, were more significant and revealed closer correlation with the clinical course than did the variations in the serum protein concentration. In 3 cases also there was good parallelism between the blood volume figures and the weight records (Cases I, III, VI).

There is no doubt that large amounts of protein nourishment can be administered with hydrolysates and that in some patients with far advanced tuberculosis and significant weight loss a protein deficiency pattern can be favorably modified. Such patients are also frequently anemic and blood transfusions are an asset. Mixtures of amino acids will not improve the anemia at first, although they most likely aid later in the elaboration of hemoglobin. Transfusion therapy was omitted from this study so that the hyperalimentation program per se could be properly appraised. It was not the intention to undertake a therapeutic comparison of the hydrolysate preparations. Their use entails some objectionable features. Four patients (Cases II, III, IV, V) had gastro-intestinal disturbances of nausea, vomiting and/or diarrhea which in only 2 cases, however, were of moderate severity. The earlier experience also indicated that in 2 patients with frank symptoms of associated intestinal tuberculosis, the oral use of hydrolysates aggravated these symptoms. It is probable that the above untoward manifestations may be lessened by gradually increasing the dose of the hydrolysate up to the required level rather than starting immediately with the total prescribed quantity. The unpleasant taste of these products is a personal equation and can be masked somewhat by the addition of peppermint water. Most of the patients commented at times about the monotony of hydrolysate therapy and experienced some loss of appetite for natural foods but these complaints were not presented as serious disadvantages.

A basic question is whether the normal intake of a natural high protein diet may not accomplish what the hyperalimentation method sets out to do. The writers' past experience, though limited, has indicated that in tuberculous patients of poor general condition and extensive disease, the prolonged use of a diet containing 150 Gm. or more of whole protein is frequently tolerated with difficulty as the bulk is too great and the sense of fullness and satiation too discomforting. As mentioned previously, much more protein and in smaller bulk can be supplied in the hydrolyzed form than as whole protein. Furthermore, the hydrolysates provide a more uniform composition and their intake can be calculated more readily. Another advantage is that the hydrolysates spare the need for protein digestion. No direct evidence is available, however, to prove that in tuberculosis there is a failure to break down proteins into amino acids; significant enzymic dysfunction of the gastric and pancreatic juices has not been demonstrated. It therefore appears probable that protein concentrates, unhydrolyzed preparations, such as casein, wheat germ, soy bean flour or commercially available processed proteins, can be of value. These products have the added advantages of increased palatability, economy and lessened gastro-intestinal irritation.

SUMMARY

Protein hydrolysates containing varying amounts of amino acids were used orally to supplement the regular hospital diet in 6 tuberculous patients who had shown an unfavorable clinical or roentgenological course. The dietary therapy was continued for six to eleven months. Four of the surviving patients were then returned to the routine diet and were observed during a six month control period.

During hyperalimentation, 3 patients gained weight and the beneficial effect was attributed primarily to the therapy. The pulmonary lesions of these patients were either improved or stationary, as determined by roentgenography. One patient died suddenly. Of the two living patients, one lost and the other continued to gain weight after the regular diet alone was resumed. The remaining 3 patients (one died) lost weight during hydrolysate therapy and showed evidence of progression of their tuberculosis. After resumption of the regular diet, one patient lost and the other gained weight.

Tuberculous patients who show evidence of clinical deterioration, or in whom it may be desirable to attempt improvement of the nutritional status preliminary to or after thoracic surgery, may be suitable subjects for hyperalimentation with particular emphasis on increased protein. The advantages and disadvantages of the oral use of protein hydrolysates are discussed.

SUMARIO

La Proteohidrolisatoterapia Oral Complementaria en la Tuberculosis

Empleáronse por vía bucal hidrolisatos de proteína que contenían distintas cantidades de amino-ácidos esenciales para complementar la habitual alimentación hospitalaria en 6 tuberculosos que habían mostrado una evolución clínica o roentgenológica desfavorable. La dietoterapia continuó de seis a once meses. Cuatro de los sobrevivientes fueron entonces puestos de nuevo a la dieta corriente y observados durante un período de comprobación de seis meses.

Durante la hiperalimentación, 3 enfermos aumentaron de peso, atribuyéndose el beneficio primordialmente al régimen empleado. Según determinó la radiografía, las lesiones pulmonares de estos enfermos o bien mejoraron o se estacionaron. Un enfermo murió repentinamente. De los dos vivos, uno perdió y el otro continuó ganando peso después de reanudarse la dieta regular sola. Los otros 3 enfermos (uno murió) perdieron peso durante la hidrolisatoterapia y revelaron signos de agravación de su tuberculosis.

Los tuberculosos que revelan signos de deterioro clínico, o en los que puede convenir tratar de mejorar el estado nutritivo antes o después de la cirugía torácica, pueden constituir sujetos apropiados para la hiperalimentación, haciendo en particular hincapié en un aumento de proteína.

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NINETY CONSECUTIVE CASES OF PULMONARY TUBERCULOSIS TREATED BY A COMBINATION OF STREPTOMYCIN AND PNEUMOTHORAX[1,2]

GEORGE A. HYMAN AND STANLEY H. HOFFMAN

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INTRODUCTION

In this article 90 consecutive cases of pulmonary tuberculosis, treated at Fitzsimons General Hospital during the years 1946–1948 with a combination of pneumothorax and streptomycin, are presented. In a separate communication (1) the writers have attempted to evaluate another type of collapse procedure, pneumoperitoneum, in connection with streptomycin.

Because of the inadequate results frequently obtained following the use of streptomycin alone (2, 3, 4, 5), the writers became interested in combining temporary collapse measures with streptomycin therapy. The purposes of these additional measures are twofold: (*1*) to maintain closure of cavities and promote their healing; (*2*) to obtain closure of cavities that did not close or could not be expected to close on streptomycin alone.

It is considered to be extremely important that cavity closure be obtained as soon after the initiation of streptomycin therapy as possible because of the high percentage of cases in which drug-resistant strains of tubercle bacilli emerge (6). At the Fitzsimons General Hospital this phenomenon occurred in 36 per cent of a series of patients who received 2 Gm. of streptomycin daily and in 29 per cent of a group treated with 1 Gm. daily. The combined series totalled 361 patients.

If each step in the therapeutic plan be carefully thought out, succeeding measures will not be jeopardized by overzealous but ill-advised or untimely use of streptomycin. It has become obvious from experience at Fitzsimons General Hospital that it is most advantageous to use a short course of streptomycin as early in the treatment as possible, to be followed by other measures if this is not definitive. Otherwise, in the face of drug resistance, if surgery is required it must be performed without chemotherapeutic protection against spread of the infection (7).

The same criteria for selection of collapse procedures, as recommended by Rafferty (8), were used in the cases of the present study as in nonstreptomycin treated cases.

It is believed that the trend of treatment of cavitary lesions in pulmonary tuberculosis is changing toward the use of streptomycin in conjunction with some type of collapse measure, as demonstrated by the following evaluation of 90 cases treated by the combined method.

[1] From the Medical Service, Fitzsimons General Hospital, Denver, Colorado.

[2] Published with permission of The Surgeon General, U. S. Army, who assumes no responsibility for the opinions expressed or conclusions drawn by the authors.

PLAN OF INVESTIGATION

Criteria for the selection of cases: The series consisted of 90 consecutive cases who underwent treatment for pulmonary tuberculosis at Fitzsimons General Hospital during the years 1946–1948. No special selection was made and all of the cases available at the time for study were included. The majority of the patients in the series were young white males on active duty in the armed forces or recently discharged. It is realized that for accurate evaluation of the treatment for pulmonary tuberculosis long term studies are necessary and that the cases in this series represent for the most part a short term observation, averaging approximately ten months. This is a consequence of the fact that patients are hospitalized at Fitzsimons General Hospital for only a relatively short period before being discharged to Veterans Hospitals. It is believed that reporting the results of this study is justified at this time because significant improvement occurred in only a few months.

All patients were maintained on absolute bed rest or bed rest with lavatory privileges. This was taken into consideration in interpreting the results, and in the cases evaluated as "good" or "excellent" the results definitely surpassed those which would normally be expected on bed rest alone.

Streptomycin regimens: Streptomycin was administered in the following schedule of doses: Forty-nine patients received 1 Gm. per day divided into 2 daily doses intramuscularly. The total duration of therapy in these cases ranged between one and four months but the majority were treated for two or three months. Thirty-two patients received 2 Gm. per day divided into 5 daily doses intramuscularly. In general, this dose was administered for a total period of four months. In 9 cases, however, the duration of therapy varied from two to eight months. In addition to the intramuscularly administered streptomycin, 4 patients received the drug as an aerosol. There were 3 patients who received experimental doses of streptomycin, each respectively receiving 2 Gm. every three days; 2 Gm. every five days; 0.5 Gm. every day; for a total of 120 days. The results obtained in these cases compared favorably with those receiving the standard dosages.

Toxic Reactions: In 2 patients receiving 1 Gm. per day, streptomycin was discontinued because of severe dermatitis, but the period of treatment was considered to be adequate. On the 1 Gm. per day dosage, 5 additional patients had mild symptoms, 2 moderate and 40 had no symptoms. Of the 38 patients on 2 Gm. per day dosage, 18 had no symptoms, 12 had mild symptoms and 8 moderate symptoms. The 3 patients on miscellaneous dosages developed no toxic symptoms.

The aim was to obtain adequate pneumothoraces in all cases as prescribed by Rafferty (8) and Alexander (11). In no case was positive pressure or marginal pneumothorax given. Twelve patients received a closed intrapleural pneumonolysis and one patient received an open pneumonolysis. Ten of these were successful, resulting in a good to excellent collapse and 3 were unsuccessful but the pneumothorax was maintained.

Three patients received a concurrent pneumoperitoneum and 8 patients received a phrenemphraxis on the pneumothorax side.

Six patients received pneumothorax on the less involved side as a preparatory measure for thoracoplasty for the more diseased lung.

Three patients received bilateral pneumothorax.

Two patients were pregnant and had uncomplicated deliveries while under study.

Bronchoscopy was performed in 45 of the cases or 50 per cent. Indications for bronchoscopy were as prescribed by McIndoe, Steele, *et al.* (12), and Sharp and Gorham (24).

The pneumothoraces were graded as "excellent," "good," "fair," and "poor." A pneumothorax was considered "excellent" if no adhesions were present and an adequate collapse was maintained. If a small adhesion was present that did not interfere with the collapse, the pneumothorax was considered as "good." In those cases where an apparently adequate pneumothorax was present in spite of adhesions the pneumothorax was considered "fair." The classification as a "poor" pneumothorax is self-explanatory.

Twenty-two pneumothoraces were classified as "excellent," 34 as "good," 18 as "fair," and 16 as "poor."

The roentgenographic results were classified into five categories. These were "excellent," "good," "fair," "slight," "no change or worse." A spectacular roentgenographic clearing plus cavity closure was graded as "excellent." A grade of "good" was given if marked roentgenographic regression occurred that was superior to that expected on bed rest but where cavity closure was not as prompt or as complete as in the "excellent" cases. Results which were better than normally anticipated on bed rest were classified as "fair." The remaining two categories, "slight" or "no change" are self-explanatory.

The grading of improvement in clinical symptoms closely follows that used for the classification of roentgenographic regression. Cough, sputum production, weight, toxicity, and erythrocyte sedimentation rate were the factors taken into consideration. Roentgenograms, sputum examinations, and erythrocyte sedimentation rates and weight determinations were obtained at monthly intervals. Cultures of the gastric washings and special roentgenograms were obtained whenever indicated.

There was only one minimal case of pulmonary tuberculosis in the series. Of the cases, 54 or 60 per cent were moderately advanced and 35 or 39 per cent were far advanced. The average period of observation was approximately ten months, the shortest being four

TABLE 1

Combined Treatment with Streptomycin and Pneumothorax

	TOTAL	SEX		COLOR			AGE				N. T. A. CLASSIFICATION		
		Male	Female	White	Colored	Others	Teen to 19	20 to 29	30 to 39	Over 40	Min.	Mod. Adv.	Far Adv.
Number	90	84	6	76	11	3	20	49	16	5	1	54	35
Percentage	100	93	7	85	12	3	22	54	18	6	1	60	39

TABLE 2

Combined Treatment with Streptomycin and Pneumothorax

	STREPTOMYCIN FOLLOWED BY PNEUMOTHORAX	STREPTOMYCIN AND PNEUMOTHORAX SIMULTANEOUSLY	PNEUMOTHORAX FOLLOWED BY STREPTOMYCIN
Total	50	15	25
Percentage	55	17	28

months and the longest four years. Every effort was made to be extremely conservative in the evaluation of these cases.

The efficacy of streptomycin in the treatment of moderately advanced and far advanced cases of pulmonary tuberculosis has been well demonstrated by many investigators (3, 10, 13, 14 and 25).

Rapid spontaneous regression was not likely to occur in these patients as they had received a course of bed rest therapy without regression prior to the institution of combined treatment.

Of the 90 patients treated, 76 were white, 11 were Negroes, and 3 were Chinese or Japanese. Eighty-four were males and 6 were females. The largest age group was between 20 and 29 which included 49 of the cases, and 20 were in their teens. Sixteen were between the ages of 30 and 39. Only 5 of the patients were over 40.

The series is divided into 3 groups. The first and largest group consisting of 50 cases, or 55 per cent, are those cases treated with streptomycin for at least one month prior to the induction of the pneumothorax. The second group consists of 15 cases, or 17 per cent, which had pneumothorax and streptomycin started simultaneously. In all cases in this group

both modes of treatment were started within a few days of each other. Twenty-five, or twenty-eight per cent, constituted the third series in which pneumothorax preceded streptomycin by more than one month. This threefold classification was made to evaluate the different therapeutic results that could be obtained from the various combinations (table 2).

RESULTS

Streptomycin Therapy Instituted Prior to Pneumothorax (50 cases)

The patients who were treated with streptomycin before the induction of pneumothorax continued to receive the drug for several days to several months following the start of collapse therapy. In 34 of this group, reversal of infectiousness had occurred at the time the information for this article was collected. Tubercle bacilli remained present in the sputum of 8 of these patients while they received only streptomycin, but the bacilli disappeared following induction of pneumothorax. Sixteen, or 32 per cent, of the patients continued to discharge tubercle bacilli in the sputum (table 3A).

Cavity closure was observed in only 5 cases on streptomycin alone. Forty-five had visible cavitation on the roentgenogram before pneumothorax was induced and in 19 of these patients the cavities closed following collapse therapy. Cavity closure occurred four times as frequently after pneumothorax was induced as while streptomycin therapy was used alone.

Cavities persisted in 26 patients after combined therapy, and the discharge of tubercle bacilli in the sputum continued in 16. In the group in which cavity closure was obtained, it was found that reversal of infectiousness frequently preceded the cavity closure by one to three months.

In Table 3B it may be seen that 11 of the 16 patients without "sputum conversion" have been followed for less than four months and that 20 of 26 patients who failed to experience cavity closure have also been followed for less than four months after institution of combined treatment. A further review at the end of six months of combined treatment would be especially valuable as Bendove *et al.* (15) show that 90 per cent of 546 cases becoming negative after pneumothorax had been induced did so by the end of the first semester.

Further comparison of the cases in which cavity closure occurred with those in which cavities persisted reveals that in the former group 18 had only moderately advanced lesions and 6 had far advanced lesions. In the group without cavity closure 13 cases were moderately advanced and 13 were far advanced. The ratio of moderately advanced to far advanced was 3 to 1 in the more successful group as compared to a 1 to 1 ratio in the less successful group. In retrospect the preferred type of treatment in several of these cases of far advanced disease without cavity closure may have been pneumoperitoneum rather than pneumothorax. Moreover, 6 of the cases without cavity closure were being prepared for thoracoplasty. The pneumothorax was maintained on the less diseased side and could not be expected to have any effect on the contralateral cavitary disease.

A total evaluation of this group reveals that 36, or 72 per cent, had either "good" or "excellent" roentgenographic improvement and that 32 or 64 per

cent had "good" or "excellent" clinical improvement. Only 3 patients showed no roentgenographic improvement or became worse and only one case failed to show any clinical improvement.

TABLE 3A

Streptomycin Instituted Prior to Pneumothorax
Reversal of Infectiousness and Cavity Closure

Before Combined Treatment

"Sputum conversion" on streptomycin alone	26 (52%)	Cavity closure on streptomycin alone	5 (10%)
No "sputum conversion" on streptomycin alone	24 (48%)	No cavity closure on streptomycin alone	45 (90%)
Total	50 (100%)	Total	50 (100%)

After Combined Treatment

"Sputum conversion" after pneumothorax added	34 (68%)	Cavity closure after pneumothorax added	24 (48%)
No "sputum conversion" after pneumothorax added	16 (32%)	No cavity closure after pneumothorax added	26 (52%)
Total	50 (100%)	Total	50 (100%)

TABLE 3B

Streptomycin Instituted Prior to Pneumothorax
Duration of Follow-up after Combined Treatment in Patients Without "Sputum Conversion" or Cavity Closure

	TOTAL	FOLLOW-UP—NUMBER OF MONTHS				
		1 to 2	2 to 3	3 to 4	4 to 6	6 to 9
No "Sputum Conversion"	16	0	6	5	2	3
No Cavity Closure	26	6	8	6	4	2

TABLE 3C

Streptomycin Instituted Prior to Pneumothorax
Cavity Closure

	TOTAL	MODERATELY ADVANCED		FAR ADVANCED		MORE THAN 50 PER CENT	LESS THAN 50 PER CENT
		Number	Per cent	Number	Per cent	Decrease in Cavity Size	Decrease in Cavity Size
Cavity Closure	24	18	75	6	25	Complete	Complete
No Cavity Closure after Combined Treatment	26	13	50	13	50	13 (50)	13 (50)

A comparison is shown in Table 4B between the adequacy of pneumothorax and the final results. It can be seen that there is a direct correlation between

the type of pneumothorax and the results as would normally be expected. Thirty-eight of the 50 cases showed "excellent" or "good" final results. Of these 29 had "good" or "excellent" pneumothoraces and 6 had a "fair" collapse.

Streptomycin and Pneumothorax Started Simultaneously

Pneumothorax and streptomycin were started at the same time in 15 cases. In 11 of these patients, tubercle bacilli disappeared from the sputum and in 10 cavity closure occurred. Of the 4 in whom "sputum conversion" did not

TABLE 4A

Group I: Streptomycin Instituted Prior to Pneumothorax
Total Evaluation at End of Observation Period

	TOTAL	"EXCELLENT"	"GOOD"	"FAIR"	"SLIGHT"	"NONE" OR "WORSE"
Roentgenographic Improvement	50	13 (26%)	23 (46%)	10 (20%)	1 (2%)	3 (6%)
Clinical Improvement	50	8 (16%)	24 (48%)	13 (26%)	4 (8%)	1 (2%)*

* One patient asymptomatic at start of therapy.

TABLE 4B

Group I: Streptomycin Instituted Prior to Pneumothorax
Final Evaluation of Results Correlated with Adequacy of Pneumothorax

FINAL RESULTS	NUMBER	PER CENT	TYPE OF PNEUMOTHORAX			
			"Excellent"	"Good"	"Fair"	"Poor"
"Excellent"	16	32	6	5	4	1
"Good"	22	44	2	16	2	2
"Fair"	7	14	2	2	2	1
"Slight"	2	4	0	0	2	0
"None" or "Worse"	3	6	0	0	1	2
Total	50	100	10	23	11	6

occur, 3 were followed for less than 4 months. The same short period of observation applied to 4 of the 5 patients in whom cavity closure did not occur. Twelve of the 15 cases, or 80 per cent, experienced either "excellent" or "good" roentgenographic results and 10, or 67 per cent, showed "excellent" or "good" clinical improvement (table 5B).

In the total evaluation of these cases, 9 were considered as having attained "excellent" results; 3, "good" results; 2, "fair" results, and one became worse.

Pneumothorax followed by Streptomycin

Twenty-five patients received pneumothorax prior to the start of streptomycin therapy. This series is comprised of two main groups: (*1*) those cases in whom pneumothorax alone had not produced adequate therapeutic results, and (*2*)

those cases in which streptomycin was added shortly after pneumothorax was induced. In all of these cases pneumothorax was continued after streptomycin was given.

Of the 25 cases, "sputum conversion" occurred in 5 on pneumothorax alone. In an additional 13 cases the sputum became negative for tubercle bacilli (culture) after streptomycin was added. In only 6 cases did the sputum remain positive for tubercle bacilli. A direct parallel can be drawn in regard to cavity closure. On pneumothorax alone, only 5 cases showed cavity closure on the roentgenogram, whereas an additional 12 had closure after streptomycin was

TABLE 5A

Streptomycin and Pneumothorax Started Simultaneously (15 cases)
"Sputum Conversion" and Cavity Closure

	NUMBER	PER CENT
"Sputum Conversion"		
Yes	11	73
No	4	27
Total	15	100
Cavity Closure		
Yes	10	67
No	5	33
Total	15	100

TABLE 5B

Streptomycin and Pneumothorax Started Simultaneously
Total Evaluation at End of Observation Period

	TOTAL	"EXCELLENT"	"GOOD"	"FAIR"	"SLIGHT"	"NONE" OR "WORSE"
Roentgenographic Improvement	15	6	6	2	1	0
Clinical Improvement	15	5	5	4	1	0

added. In 8 cases, visible cavitation persisted, but 4 of these have been followed for less than four months since combined therapy was instituted (table 6A).

Roentgenographic improvement was "excellent" in 5 cases, "good" in 11 cases, and 8 showed "fair" improvement. Only one case showed "slight" improvement and none became "worse".

A final, complete evaluation revealed that "excellent" clinical improvement occurred in 6 patients and 8 were classified as "good." Eight patients showed a "fair" improvement and 3 failed to improve (table 6B).

Nine patients in this group had what was considered an "excellent" pneumothorax and in 7 the collapse was considered as "good". Of these 16 patients,

TABLE 6A

Pneumothorax Induced Prior to Streptomycin Therapy
"Sputum Conversion" and Cavity Closure

Before Combined Treatment

"Sputum conversion" on pneumothorax alone	5 (20%)	Cavity closure on pneumothorax alone	5 (20%)
No "sputum conversion" on pneumothorax alone	19* (76%)	No cavity closure on pneumothorax alone	20 (80%)
Total	25 (100%)	Total	25 (100%)

After Combined Treatment

"Sputum conversion" after addition of streptomycin	18 (72%)	Cavity closure after addition of streptomycin	17 (68%)
No "sputum conversion" after addition of streptomycin	6* (24%)	No cavity closure after addition of streptomycin	8 (32%)
Total	25 (100%)	Total	25 (100%)

* In one patient with cavity, sputum and gastric washings were negative for tubercle bacilli throughout entire period of observation.

TABLE 6B

Pneumothorax Induced Prior to Streptomycin
Total Evaluation at End of Observation Period

	TOTAL	"EXCELLENT"	"GOOD"	"FAIR"	"SLIGHT"	"NONE" OR "WORSE"
Roentgenographic Improvement	25	5	11	9	0	0
Clinical Improvement	25	6	8	8	3	0

TABLE 6C

Pneumothorax Induced Prior to Streptomycin
Final Evaluation of Results Correlated with Adequacy of Pneumothorax

FINAL RESULTS	NUMBER	PER CENT	TYPE OF PNEUMOTHORAX			
			"Excellent"	"Good"	"Fair"	"Poor"
"Excellent"	11	44	4	5	2	—
"Good"	9	36	3	2	1	3
"Fair"	2	8	1	—	1	—
"Slight"	2	8	1	—	—	1
"Poor"	1	4	—	—	—	1*
Total	25	100	9	7	4	5

* Patient was AWOL frequently.

9 had "excellent" and 5 had "good" final results which also shows a clear correlation between results and the type of pneumothorax. In summary, 20 of the 25 patients, or 80 per cent, showed "good" or "excellent" final results when streptomycin was added to pneumothorax (table 6C).

TABLE 7

Bronchoscopy (45 of 90 cases)

	STREPTOMYCIN PRIOR TO PNEUMOTHORAX	STREPTOMYCIN AND PNEUMOTHORAX SIMULTANEOUSLY	PNEUMOTHORAX PRIOR TO STREPTOMYCIN	TOTAL
Total Bronchoscoped	27	2	16	45 (100%)
Endobronchial Disease				
No	14	1	8	23 (51%)
Yes	13	1	8	22 (49%)
Cured	10	—	8	18 (82%)
Improved	2	—	—	2 (9%)
Unchanged	1	1	—	2 (9%)

FIG. 1a. (Left) Case 1(a) before combined treatment; duration of disease for three months. Three large cavities are present in left upper lung.

FIG. 1b. (Right) Case 1(b) seven months after institution of simultaneous treatment with streptomycin (2 Gm. per day for 120 days) and left pneumothorax. The cavitation is no longer visible and there is marked clearing of the infiltration in the left lung. Last sputum positive for tubercle bacilli was in May, 1947.

BRONCHOSCOPY

Since 45 patients were bronchoscoped in this series, it is considered worth while to devote a paragraph to the findings. In 22 of the 45, or approximately 50 per cent of the cases, the typical findings of endobronchial tuberculosis were found. Three categories of endobronchial tuberculosis were designated: (*1*) submucosal, with a yellow productive nodularity on a reddened mucosa; (*2*)

FIG. 2a. (Left) Case 2(a) before combined treatment; duration of disease for four months. Massive involvement of lower two-thirds of left lung with 3 cm. cavity in midlung field and a 3 cm. cavity in left hilar region.

FIG. 2b. (Right) Case 2(b) seven months after institution of combined therapy; left pneumothorax induced January 13, 1947. Streptomycin started February 17, 1947 (2 Gm. per day for 120 days). Last sputum positive for tubercle bacilli was in May, 1947.

FIG. 3a. (Left) Case 3(a) before combined treatment; duration of disease for three months. Bilateral exudative-productive disease present involving all lobes of the left lung and right upper lung; 3 cm. cavity in left upper lung.

FIG. 3b. (Right) Case 3(b) seven months after institution of simultaneous treatment with streptomycin (2 Gm. per day for 150 days) and left pneumothorax. The cavity is no longer visible in the left upper lung and there is almost complete clearing of both lung fields. Last sputum positive for tubercle bacilli was in April, 1947.

ulcerative, showing a velvety, granular base with ulceration; and (3) fibrostenotic. The diagnosis was usually made on the basis of one examination. After treatment with streptomycin, 18 of the 22 patients, or 82 per cent, showed no evidence of endobronchial disease on bronchoscopy and 2 showed healing lesions. In two instances the lesions were unchanged as determined by bronchoscopy. The majority of the cases of endobronchial disease were present in the group which received streptomycin prior to pneumothorax. Thus the antibiotic treatment made it possible for an effective pneumothorax to be induced. In several other patients in whom tension cavities developed while receiving pneumothorax, streptomycin was instrumental in controlling the endobronchial tuberculosis and thereby promoting healing of the parenchymal lesion.

DISCUSSION

The writers are aware of the difficulty of evaluating the role played by either streptomycin or pneumothorax alone in the treatment of pulmonary tuberculosis and realize that it is even more difficult to attempt to evaluate the role played by each when they are used together. In addition cavity closure does not necessarily mean healing (7). It is believed, however, that by analyzing the results in this series certain deductions can be made.

It might be assumed when streptomycin was used first and followed by pneumothorax, that the therapeutic burden was carried by the antibiotic. The results seem to definitely indicate, however, that this is not the case. In the group in which streptomycin was used first, only 5 cavities closed on streptomycin alone. In an additional 19 cases, cavity closed roentgenologically after pneumothorax was added to the treatment, which represents a fourfold increase in closure. Other investigators who have used streptomycin alone in the treatment of cavitary disease report that it is not adequate treatment for obtaining permanent closure. D'Esopo (2) states "X-ray films of 11 of 14 patients revealed a reduction in size of cavities during the first 2 months of streptomycin therapy, but in only 1 instance did unequivocal cavity closure occur." In addition, the same writer and others have found that streptomycin-resistant tubercle bacilli appear in a high percentage of patients with persistent cavitary disease. It has also been the experience at Fitzsimons General Hospital, as well as that of other investigators, that a significant number of cavity closures occurring on streptomycin alone reopen after the streptomycin is discontinued (2). Therefore the writers are in agreement with D'Esopo (2) who believes "That there might be an optimum time during the course of streptomycin therapy when the institution of collapse procedures might have preserved what improvement had occurred."

Although pneumothorax itself is an accepted method of treatment for cavitary disease in pulmonary tuberculosis, as is borne out by numerous investigators (16, 17), this series demonstrates that in many cases pneumothorax produced optimum results only after streptomycin had been added. This was shown by the group of 25 pneumothorax cases in which streptomycin was given as an adjunct. Only 5 of these cases experienced cavity closure on pneumothorax alone, whereas

an additional 12 experienced cavity closure when streptomycin was added. A strikingly comparable result was seen in the reversal of infectiousness.

Nine of the 18 cases which eventually showed "sputum conversion," had been maintained on pneumothorax from four to twelve months prior to the addition of streptomycin therapy. Eight of these 9 "converted" their sputum within the first two months after streptomycin was added to the pneumothorax. This indicates the role of the combined treatment in hastening the healing of an otherwise sluggishly responding process.

Excellent results were also obtained in a smaller group in which the combination of streptomycin and pneumothorax was introduced simultaneously. Eleven of the 15 cases "converted" their sputum and 10 obtained cavity closure. This further bears out the efficacy of combined treatment.

Long term observations will be necessary to determine the optimum time either for introducing pneumothorax as an adjunct to streptomycin or streptomycin as an adjunct to pneumothorax in cavitary disease. Even at this early stage, however, certain factors can be recognized.

Pneumothorax has been shown to decrease the circulation of the collapsed lung by Dock (18). It is theoretically possible, therefore, that streptomycin should be given for several weeks prior to the induction of the pneumothorax in order to obtain maximum streptomycin concentration in the diseased tissue.

It appears probable that, if a pneumothorax is introduced while the patient is receiving streptomycin, a certain amount of protection against post-induction empyema and spread of disease is afforded. In the 65 cases presented in this series in which "protection" was given by streptomycin at the time of induction, no case of extension of disease or empyema occurred. In pre-streptomycin days, empyema usually occurred in 5 to 10 per cent of the cases in which pneumothorax was maintained and extension of the pulmonary disease occurred in an appreciable number. Gibbons (19) reports that 10.2 per cent of 663 cases developed empyema during pneumothorax treatment. The usual incidence of purulent effusion occurring during pneumothorax is discussed by Weisman (20). In 72 of 150 patients, pleural effusion was noted following the induction. Thirty-three effusions were aspirated of which 10 were originally purulent, and an additional 7 later became purulent. The peak incidence of effusions was reached early in the third month.

Streptomycin has been demonstrated to be most effective if introduced early in the course of the disease. The exudative stage of the lesion is most prominent at this time and this is known to respond best to streptomycin (21). This must be taken into consideration before inducing a pneumothorax alone, in that the exudative element will gradually comprise a smaller percentage of the pathological process as time elapses. If it is then found that a pneumothorax is incapable of healing the disease alone, introduction of streptomycin may not be as efficacious as it would have been much earlier in the disease process.

It seems to the authors that the above mentioned facts and data indicate that in the majority of cases the optimum treatment of pulmonary tuberculosis with cavitation will result from a course of streptomycin started several weeks before

the induction of the pneumothorax. The streptomycin should be continued for one to two weeks following the induction of the pneumothorax and in almost all cases the entire course of streptomycin therapy should comprise approximately six weeks of treatment at 1 Gm. per day intramuscularly (22).

In the entire series of 90 cases, 70 patients, or 78 per cent, had "excellent" or "good" final results. Of these, 50 had "excellent" or "good" pneumothoraces and an additional 11 were classified as "fair." Thus there is seen to be a very definite correlation between the adequacy of pneumothorax and the final therapeutic results. This in itself substantiates the value of pneumothorax in the combined method.

Not only can good final therapeutic results be obtained in a large percentage of cases, but a further type of application of the combined method is seen in a group of 6 cases of far advanced disease where prognosis had previously been hopeless. In each of these 6 cases a short course of streptomycin was given as well as pneumothorax. The combination was effective in preparing these cases for a thoracoplasty on the more involved side. The ultimate salvage of these cases is a tribute not only to streptomycin but to its judicious use in a well planned therapeutic approach to each individual case.

It has been the policy at Fitzsimons General Hospital to outline the tentative plan of treatment for each case of pulmonary tuberculosis. One of the first steps in the plan is a bronchoscopy. This was performed in 45 of the 90 cases and revealed a 50 per cent incidence of endobronchial tuberculosis. The presence of endobronchial tuberculosis acts as one of the determinants for the use of streptomycin as a first step in the plan of treatment. This then safeguards the subsequent induction of a pneumothorax (23).

In evaluating the end results of a planned method of treatment utilizing a combination of streptomycin and pneumothorax, the following significant data were obtained. Eighty-nine of the 90 cases had sputum positive for tubercle bacilli prior to therapy. Of these, 63 "converted." Cavity closure was attempted in 84 cases and 51 had successful roentgenographic closure. There were 6 other patients of the original 90 who did not receive pneumothorax on the side with the cavitary disease, but were being prepared for thoracoplasty by a contralateral pneumothorax. The average period of observation for the entire series was ten months. Although these 90 cases of combined treatment represent a short term study, it is believed that the results are significant and indicate a new trend in the therapy of pulmonary tuberculosis.

SUMMARY

The results of a study of ninety consecutive cases of pulmonary tuberculosis treated at Fitzsimons General Hospital from 1946 to 1948 with intramuscular streptomycin and pneumothorax are presented. One case of minimal pulmonary tuberculosis, 54 moderately advanced lesions and 35 far advanced cases were studied in the series. The results indicate that a combined method of treatment employing pneumothorax and streptomycin is a very effective means of treatment for pulmonary tuberculosis.

SUMARIO

Noventa Casos Consecutivos de Tuberculosis Pulmonar Tratados con una Combinación de Estreptomicina y Neumotórax

El estudio presentado versa sobre 90 casos consecutivos de tuberculosis pulmonar tratados en el Hospital General Fitzsimons de 1946 a 1948 con estreptomicina intramuscular y neumotórax. La serie comprendió un caso de tuberculosis pulmonar mínima, 54 lesiones moderadamente avanzadas y 35 casos muy avanzados. El resultado indica que un método terapéutico que combina el neumotórax y la estreptomicina ofrece un medio muy eficaz de tratamiento para la tuberculosis pulmonar.

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THE EFFECT OF STREPTOMYCIN, PARA-AMINOSALICYLIC ACID (PAS) AND THEIR COMBINATION ON THE TUBERCLE BACILLUS IN VITRO AND IN VIVO[1,2,3]

ROBERT G. BLOCH, KIRSTEN VENNESLAND, ROBERT H. EBERT AND GEORGE GOMORI

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INTRODUCTION

Para-aminosalicylic acid (PAS) as a bacteriostatic agent against the tubercle bacillus was suggested by Lehmann (1, 2), who based his investigations on the work of Bernheim (3). The latter had observed that the sodium salts of benzoic and salicylic acids specifically stimulated the oxygen uptake of the organism. The tuberculostatic effect of PAS was quickly confirmed by Sievers (4) and by Youmans (5).

In a previous paper (6) a detailed comparison was made of the response of the tubercle bacillus *in vitro* to various concentrations of PAS, streptomycin, and the combination of these two drugs. It was found that PAS inhibited growth of both the streptomycin-sensitive strain, H-37RV, and the naturally occurring streptomycin-resistant variant, H-37RVNR1, almost completely in concentrations of 1.2 γ/cc. and partially in concentrations of 0.6 γ/cc. The inhibition of growth of H-37RV was markedly enhanced if a subinhibitory concentration of one drug was combined with a moderately inhibitory concentration of the other. This enhancement of inhibition by the combination of PAS and streptomycin was not found when it was used against the H-37RVNR1 strain. Another resistant strain, isolated from a patient following clinical treatment with streptomycin, a strain which was moderately inhibited by the highest concentration of streptomycin used (3700 γ/cc.) did, however, show the enhancement of inhibition when exposed to the combination of the two drugs.

METHODS

The *in vivo* experiments were carried out in guinea pigs. The virulent human strain of tubercle bacilli H-37RV was used to infect the animals. Each pig was inoculated subcutaneously with 0.1 mg. (wet weight) of a 2 week old culture of organisms grown in Dubos medium. Twenty-one days after infection the animals were divided into four groups and care was taken to ensure an equal distribution of animals of similar size and weight. The first group was treated with streptomycin alone, the second with PAS alone, the third with a combination of the two drugs, and the fourth was used as untreated controls. A portion of each of the first three groups was treated for 24 days and another for 45 days. A portion

[1] From the Department of Medicine, The University of Chicago, Chicago, Illinois.

[2] Presented before the Medical Section, as part of the symposium on *Chemotherapeutics and Antibiotics*, at the 44th Meeting of the National Tuberculosis Association, New York, New York, June 16, 1948.

[3] This investigation was supported by a grant from the Division of Research Grants and Fellowships of the National Institute of Health, U. S. Public Health Service.

of the control group was sacrificed at the time treatment was started to determine the extent of disease at this time, while the other control animals were killed at the end of the two treatment periods. Of the treated animals the majority (46) were sacrificed after 24 days of treatment or died within near range of that period, while 18 animals were treated for 45 days or died shortly before the termination of the experiment. The exact arrangement of the experiment with divisions made according to the length of treatment is shown in table 1.

The stroptomycin was dissolved in sterile distilled water and was given in one daily dose of 8 mg. contained in 1 cc. of solution. The PAS was carefully weighed, dissolved in distilled water, brought to a pH of 7.0 with NaOH and sterilized by passage through a Seitz filter. It was prepared in a 2.5 per cent solution and a total daily dose of 250 mg. was given by subcutaneous administration of 5 cc. of the solution twice daily. The large dose of PAS

TABLE 1

Arrangement of Experiment

70 guinea pigs inoculated subcutaneously with 0.1 mg. of tubercle bacilli (H-37RV)
Treatment begun 21 days after inoculation

EXPERIMENT	NUMBER OF GUINEA PIGS	DRUG	ROUTE	TOTAL DAILY DOSE	DISTRIBUTION	NUMBER OF DAYS OF TREATMENT
Ia	10	streptomycin	subcutaneous	8 mg.	1 dose	24
Ib	16	PAS	subcutaneous	250 mg.	2 equal doses	24
Ic	10	streptomycin and PAS	subcutaneous	8 mg. 250 mg.	1 dose 2 doses	24
IIa	7	streptomycin	subcutaneous	8 mg.	1 dose	45
IIb	Animals intended for PAS treatment in this group died prematurely and were included in Ib.					
IIc	7	streptomycin and PAS	subcutaneous	8 mg. 250 mg.	1 dose 2 equal doses	45
			Controls			
IIIa	10	Killed at beginning of treatment				
IIIb	6	Killed with Group I				
IIIc	4	Killed with Group II				

used was decided upon after consideration of the 14 to 15 Gm. daily dose used in clinical trials (1, 2, 7, 8).

Careful postmortem examinations were performed on all animals. Sections of spleen, liver, and lung were taken and both hematoxylin and eosin and acid-fast stains were made. An evaluation of the amount of tuberculosis present in each animal was made from combined study of the macroscopic and histological findings.

RESULTS

The results of treatment as compared with the findings in the control groups are presented in figures 1, 2, and 3. It may be seen from figure 1 that systemic tuberculosis was present in all control animals at the time treatment was started. It is believed that a more reliable evaluation of the effect of chemotherapeutic agents in tuberculosis is obtained if treatment of the animals is withheld until the disease has been fully established.

In figure 2, which shows the results of the short-term therapy, it is obvious that

= Grade I = Grade III

= Grade II Grade IV

FIGS. 1, 2, and 3.—An arbitrary scale of four grades of tuberculous involvement evaluated from the macroscopic extent of disease with microscopic confirmation.

The numbers under some of the animals indicate that these died spontaneously; the numbers under control animals indicate number of days after infection when death occurred; the top numbers under treated animals indicate the number of days of treatment; the bottom numbers, the number of days after infection on which death occurred.

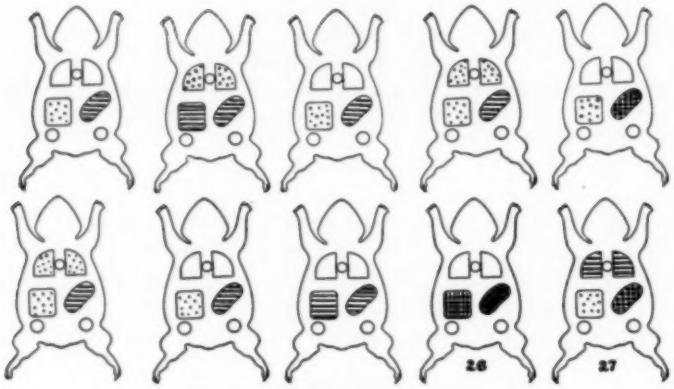

FIG. 1. Pre-treatment controls

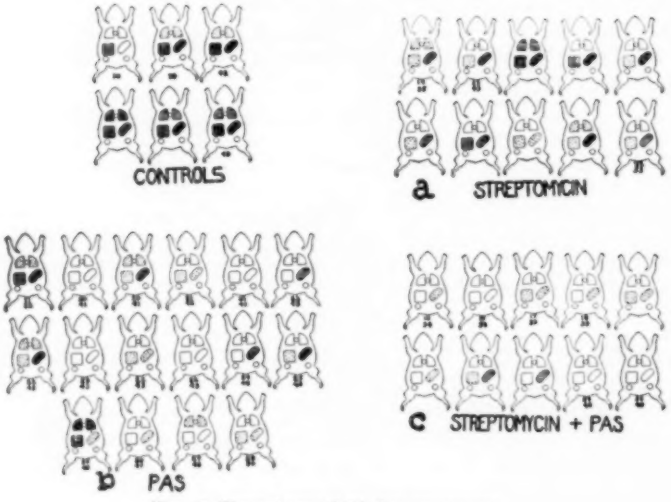

FIG. 2. Experiment I 24 day treatment

the tuberculosis in the untreated animals had continued to progress while those receiving streptomycin alone had on an average no more extensive disease than at the time treatment was started. The results in the group receiving PAS alone appear to be better than in the streptomycin group, but it must be remembered that the dose of PAS was very large (30 times that of streptomycin), so this does not indicate any superiority of PAS over streptomycin. The most striking results in the short-term treatment groups were found in the one receiving a combination of the two drugs. Only 2 animals in this group had as much as 2

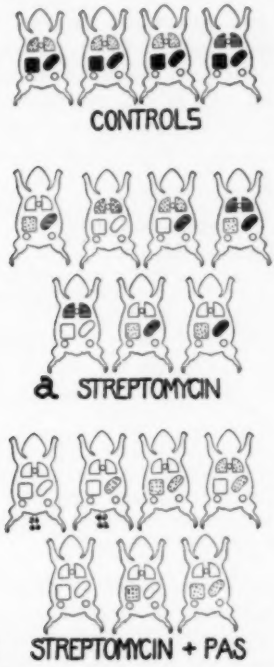

FIG. 3. Experiment II 45 day treatment

plus involvement of any organ, while the others had only minimal disease or none at all.

Figure 3 shows the results of the longer term of therapy. Again, the control animals which lived until the termination of the experiment showed further progression of the disease. Those receiving streptomycin for this length of time were beginning to show actual regression in the extent of disease, while those receiving both streptomycin and PAS showed a strikingly small amount of involvement which was no more than minimal in any of the animals.

The results of the complete experiment are expressed numerically in table 2,

which gives the average tuberculosis index for each of the groups. As in the culture experiments, the findings in animals indicate the striking inhibitory effect of the combination of the two drugs compared with that of each of the agents alone.

The microscopic as well as the macroscopic involvement of the lungs was comparatively slight even in the controls. The difference in the histologic changes between the treated groups of animals and the control groups was especially marked in the spleen and the liver.

In all the treated groups the changes were essentially the same except for the fact that they were most pronounced and frequent in the group receiving the combination of streptomycin and PAS. They consisted of two types of response. The first type was no different from the typical regressive changes seen in any case of healing tuberculosis, i.e., progressive fibrosis ending in complete disappearance of tuberculoid structure (figure 4a) and occasional calcification, especially in the spleen (figure 4b). The second type of response occurred chiefly

TABLE 2

Tuberculosis Index

Combined Macroscopic and Microscopic Findings

TREATMENT	KILLED AT BEGINNING OF TREATMENT	TREATED 24 DAYS OR DIED	TREATED 45 DAYS
Controls	4.4 (10)	7.5 (6)	8.5 (4)
Streptomycin		4.3 (10)	3.1 (7)
PAS		2.62 (16)	—
Streptomycin and PAS		1.2 (10)	1.14 (7)

The tuberculosis index is calculated from combined macroscopic and microscopic findings in the lung, liver, and spleen, grading each organ from 1 to 4. The maximum index possible is 12. The figures given are the average indices for each group. The figures in parentheses are the number of animals in the groups.

in the lungs and was similar to the changes reported by Krause (10) in anthracosis of guinea pigs. In some sections very large numbers of rounded lymphocytic infiltrates without a trace of specific reactions could be seen (figure 4c); it was impossible to decide whether all of them were residuals of pre-existing tubercles. In other sections the centers of similar structures appeared slightly lighter than the periphery so as almost to suggest germinative centers. When examined under high power, however, a number were recognized as tubercles in various phases of regression. At first the epithelioid cells showed a peculiar shrinkage, causing an early collapse of the typical architecture of the tubercle (figure 4d). At the same time a dense lymphocytic infiltrate formed at the periphery of the lesion. The center then gradually shrank to complete disappearance, leaving only a round accumulation of lymphocytes (figure 4e), with or without a few scattered giant cells. Eventually the lymphocytes too disappeared, and the only residual was a small streaky scar which was infiltrated with a few round cells. Occasionally in the liver a few giant cells singly or in small groups remained scattered without any surrounding granulation tissue (figure 4f).

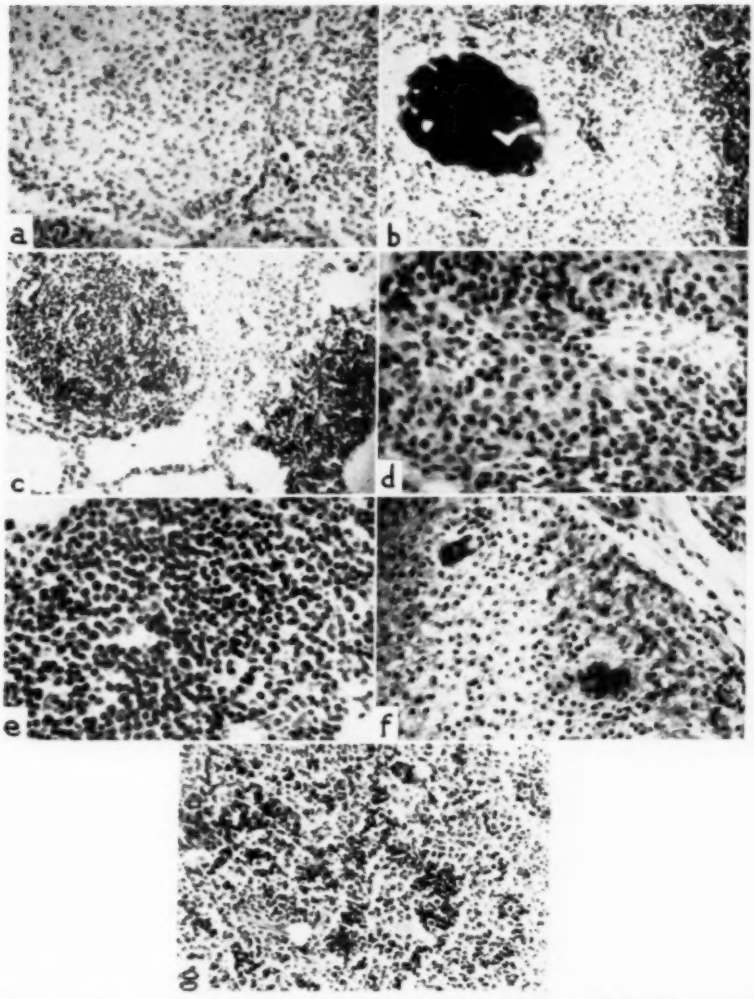

FIG. 4. a. Spleen, a completely fibrosed malpighian follicle. b. Calcification in the spleen. c. Lymphocytic accumulations in the lungs. d. Tubercle with small, shrunken epithelioid cells and peripheral lymphocytic infiltration. e. Further atrophy of epithelioid cells with complete disappearance of tuberculoid structure. f. Isolated giant cells in the liver. g. Myeloid metaplasia in spleen. Sinuses full of myeloid cells.

Another interesting finding was intense myeloid metaplasia in the spleen (figure 4g) and sometimes in the liver. Occasionally the blood in all vessels contained such large numbers of myeloid cells as are usually seen only in cases of true leukemia. Although this observation was made in 2 of the streptomycin-

treated pigs and even in one of the untreated controls, it was much more pronounced in the animals which had received PAS either alone or in combination with streptomycin. It was seen in a total of 12 such animals, 7 of which had received PAS alone and 5 the combined treatment.

The toxic effects of this large dose of PAS were considerable. Subcutaneous administration caused much local induration of the tissues and at autopsy hemorrhagic and necrotic areas were found at the sites of injection. No specific systemic lesions could be made out, but the majority of animals receiving PAS alone died before termination of the experiment. Premature death in almost all cases seemed to be due to pneumonia. It should be pointed out here that while Lehmann (2) found PAS to be highly toxic to the guinea pig, other workers (9) failed to find an excessive toxic effect from oral administration of the drug to this animal.

Smears and cultures were made from the spleens of some of the animals at the time of autopsy. Growth of tubercle bacilli in Dubos medium was obtained from 5 of these. Two had received streptomycin alone for 24 days, one had received streptomycin alone for 45 days, and 2 had received both streptomycin and PAS for 45 days. Preliminary studies on the streptomycin-sensitivity of these organisms showed that those isolated from the animals receiving the short-term streptomycin therapy were still sensitive to 0.74 γ streptomycin per cc. Those isolated from the animal receiving the long-term streptomycin therapy were resistant to 5.92 γ/cc., which was the highest concentration used in the preliminary run; while those from the 2 animals receiving the long-term combined therapy were still sensitive to 0.74 γ. Admittedly, this is too small a number of cases from which to draw any definite conclusions, but it does suggest that use of the combination of PAS and streptomycin may prevent the rapid appearance of resistant strains of tubercle bacilli.

DISCUSSION

On the basis of these *in vitro* and *in vivo* experiments with PAS and streptomycin in combination, two important clinical possibilities became apparent. First, it would seem feasible that, using a combination of the two drugs, smaller doses of streptomycin could be used effectively in the treatment of tuberculosis, thus reducing the hazard of toxic effects from this drug. Second, a delay in the emergence of streptomycin-resistance might be anticipated on theoretical grounds since PAS should be capable of suppressing growth of streptomycin-resistant strains. Insufficient evidence has been accumulated to support this view but it remains a promising possibility.

SUMMARY

1. Streptomycin alone, even in small doses given once a day and for a short period of time, will prevent the progression of tuberculosis in the guinea pig.

2. Para-aminosalicylic acid alone in large doses has a favorable effect on experimental tuberculosis.

3. The combination of streptomycin and PAS has a much more favorable effect on experimental tuberculosis in the guinea pig than either drug used alone.

SUMARIO

El Efecto de la Estreptomicina y el Acido Para-Aminosalicílico (PAS) y de la Combinación de Ambos sobre el Bacilo Tuberculoso in Vitro e in Vivo

1. La estreptomicina sola, aun a dosis pequeñas administradas una vez al dia y durante un breve período de tiempo, impide la agravación de la tuberculosis en el cobayo.

2. El ácido para-aminosalicílico solo a dosis masivas ejerce efecto favorable sobre la tuberculosis experimental.

3. La combinación de la estreptomicina y del PAS ejerce un efecto mucho más favorable sobre la tuberculosis experimental del cobayo que una u otra droga por sí sola.

Acknowledgment

The authors gratefully acknowledge the generosity of Parke, Davis & Company who supplied the para-aminosalicylic acid.

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THE EFFECT OF TUBERCLE BACILLI ON THE MIGRATION OF PHAGOCYTES IN VITRO[1]

MARTIN ALLGÖWER AND HUBERT BLOCH[2]

(Received for publication February 18, 1949)

INTRODUCTION

In previous experiments (1), the fate of living virulent and avirulent tubercle bacilli injected into the peritoneal cavity of white mice has been studied. Observations made during the first hours of infection led to the conclusion that the virulent bacilli phagocytized by the polymorphonuclear leukocytes of the exudate cause injury to the leukocytes. This results eventually in lysis of the white cells with release of the phagocytized bacilli into the peritoneal fluid. The avirulent variants of tubercle bacilli, on the contrary, did not seem to cause any injury to the leukocytes which engulfed them. After being phagocytized, they are eliminated from the exudate.

These conclusions were drawn from observations made by examining peritoneal exudates. It is the purpose of the experiments reported in this paper to study the effect of phagocytized virulent and avirulent tubercle bacilli on leukocytes in a more direct way *in vitro*. The ability of the leukocytes to migrate was chosen as a test to demonstrate a possible injurious effect of engulfed tubercle bacilli on the leukocytes. Evidence is presented that the migration of polymorphonuclear leukocytes is completely inhibited by phagocytized virulent bacilli and unaffected by avirulent variants of the same strain when tested in comparable amounts.

METHODS

All the experiments referred to in this paper were performed with two variants of one strain of human tubercle bacilli, the virulent variant H37Rv, and the avirulent variant H37Ra[3] (2). Human leukocytes were used and prepared as follows: Blood from patients with high leukocytic counts (15,000 per cu. mm. or more) was defibrinated by gentle shaking in an Erlenmeyer flask. Two and six-tenth milliliters of the defibrinated blood were placed into small test tubes and 0.4 ml. of washed bacillary suspensions were added (0.4 ml. of Tyrode solution for the control tubes). The stoppered tubes were slowly rotated for twenty minutes at 37° C. and smears made to ascertain that phagocytosis had occurred. After short centrifugation at 1,500 r.p.m. most of the supernatant fluid was discarded, 0.2 ml. of fresh chicken plasma was added and thoroughly mixed with the blood. The tubes were then centrifuged for four minutes at 4° C. and allowed to stand for twenty minutes at room temperature. At this time the buffy coat had formed a solid membrane with the clotted chicken plasma and could be removed from the tube. After repeated washings in Ringers solution it was cut into small squares of 1 to 2 mm. side length. These squares were again washed in Ringers solution.

[1] From the Department of Surgery, Bürgerspital, and the Institute of Bacteriology, University of Basel, Switzerland.

[2] Present address: The Public Health Research Institute of the City of New York, Inc.

[3] These strains, received through the courtesy of Dr. R. J. Dubos, were originally obtained from the National Tuberculosis Association Standard Culture Depot at Trudeau, N. Y., and subcultured on Tween-albumin media.

Plasma, preferably from the same patient, was prevented from clotting by keeping it at low temperature and was diluted 2:1 with cold Tyrode solution and distributed in small Carrel flasks in amounts of 2.0 ml. One square piece of buffy coat was imbedded in the center of each flask and the plasma permitted to clot at room temperature. The flasks were incubated at 37° C. and the results observed twelve to fourteen hours later.

A few experiments were carried out with leukocytes from one day old peritoneal exudates of guinea pigs or rabbits and their corresponding plasma. The results were essentially identical with those obtained with human blood.

Leukocytes prepared in the way described above and containing no bacteria keep their characteristic tendency to migrate. At the very beginning of the incubation period, the first cells can already be observed migrating radially from the square piece of buffy coat. At the end of the incubation period a halo of 2 to 4 mm. in radius surrounds the original piece. The whole culture now forms a remarkably regular round disk of 5 to 8 mm. diameter. The halo consists chiefly of polymorphonuclear leukocytes. The size of the disk varies slightly from one blood donor (or animal) to the other, but remains fairly constant within one experiment (figure 1). Since there is a close macroscopic resemblance of this preparation to an ordinary tissue culture, it may be pointed out that the halo is not composed of newly grown cells but only of leukocytes emigrating from the original piece of buffy coat (figure 2).

RESULTS

The effect of virulent tubercle bacilli on the migration of leukocytes: When leukocytes were allowed to phagocytize virulent tubercle bacilli before being implanted, their migration was inhibited. The degree of the inhibitory effect depended upon the ratio bacteria/phagocytes (table 1). In preparations where, owing to the small number of bacilli, only part of the leukocytes had a chance to phagocytize bacilli, a slight migration still occurred. It could be seen, however, that all the leukocytes which contained bacilli did not leave the center of the preparation, and that all the leukocytes found in the surrounding halo were free from bacilli. With a higher number of bacteria, inhibition was complete (figure 3).

The effect of avirulent tubercle bacilli on the migration of leukocytes: In contrast to the effect of virulent bacilli, the avirulent variant did not inhibit migration. Cells with engulfed avirulent bacilli migrated as well as the controls (figure 4). Slight inhibition occurred only if a very high number of avirulent bacilli were added to the cell suspension so that almost all of the phagocytes contained many microorganisms (table 1). The rate of phagocytosis was the same with avirulent and virulent bacilli.

The effect of dead tubercle bacilli on phagocytes: Phagocytized heat-killed tubercle bacilli of both the virulent and the avirulent variants showed essentially the same effect on the migration of leukocytes as the living bacteria.

The effect of other phagocytized material on the migration of leukocytes: Control experiments were made to study the effect of charcoal, India ink and two strains of *staphylococci* on the migration of leukocytes. Phagocytized charcoal and India

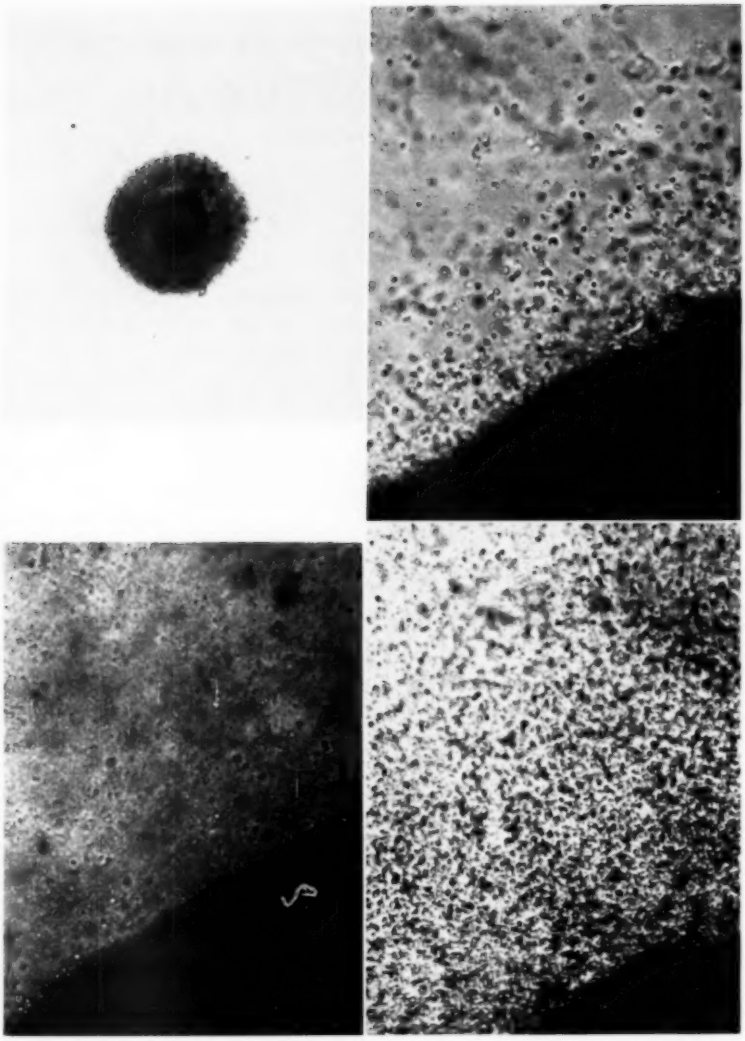

FIG. 1: (Upper left) The migration of human polymorphonuclear leukocytes after 14 hours incubation. No bacilli added. The figure shows the square piece of buffy coat imbedded in plasma, and the halo of leukocytes migrating from the original explantate. Magnification 10 ×.

FIG. 2: (Upper right) Section of a similar preparation as in figure 1 showing the edge of a young explantate with migrating leukocytes at a higher magnification (300 ×).

FIG. 3: (Lower left) The migration of human polymorphonuclear leukocytes after 14 hours incubation. Before being imbedded the leukocytes were allowed to phagocytize virulent tubercle bacilli; no migration occurred. (Magnification 300 ×).

FIG. 4: (Lower right) The migration of human polymorphonuclear leukocytes after 14 hours incubation. Before being imbedded the leukocytes were allowed to phagocytize avirulent tubercle bacilli; the migration of the cells is not inhibited by the engulfed bacilli. (Magnification 300 ×).

ink particles had no effect on the rate of migration, even when the phagocytes were heavily loaded. On the other hand, one freshly isolated strain of *St. aureus* was highly inhibitory to leukocytic migration, whereas an old laboratory strain did not affect the locomotion of the cells.

DISCUSSION

The results of these *in vitro* experiments show that virulent tubercle bacilli are injurious to polymorphonuclear leukocytes as evidenced by inhibition of the migration of the phagocytes. Since avirulent tubercle bacilli do not have a similar effect when tested in comparable number, it is likely that the inhibition of migration is in some way connected with the virulence of the bacilli. On the other hand, when a large number of avirulent tubercle bacilli is phagocytized, a slight

TABLE 1

Effect of Virulent and Avirulent Tubercle Bacilli on the Migration of Polymorphonuclear Leukocytes

STRAIN OF *M. tuberculosis*	CONCENTRATION OF BACTERIAL SUSPENSIONS	INHIBITORY EFFECT ON MIGRATION
H37Rv (virulent)	undiluted	++++
H37Rv (virulent)	1:30	++++
H37Rv (virulent)	1:90	+++
H37Rv (virulent)	1:270	+
H37Ra (avirulent)	undiluted	++
H37Ra (avirulent)	1:30	0

inhibition of migration results. This observation points to the possibility that the difference between the virulent and avirulent cultures of this strain might be quantitative rather than qualitative (2, 3)[1].

The experiments with charcoal and India ink show that indifferent particulate matter engulfed in large number by leukocytes do not inhibit their migration although a heavy charge of engulfed material might reduce or completely stop any further phagocytic activity (4).

In the present experiments, heat-killed virulent and avirulent tubercle bacilli had the same effect on migration as living ones. This action therefore seems to be caused by a cellular constituent of the virulent bacilli and does not directly depend on their multiplication.

The mechanism of the inhibitory action has not been elucidated by these experiments. It is possible that interference with locomotion can occur in the absence of other evidence of injury. The observation that large amounts of aviru-

[1] Although the H37Ra culture used did not produce a progressive disease in either guinea pigs or mice, it appeared to be a mixture of at least two variants, one of which formed clumps and the other formed weak but distinct serpentine cords in oleic acid-albumin medium. This suggests that the two variants may not be of identical virulence (Middlebrook, G., Dubos, R. J., and Pierce, C., J. Exper. Med., 1947, *86*, 175).

lent bacilli did not produce any detectable injury *in vivo* and yet can have some inhibitory action on locomotion *in vitro* points to this possibility.

SUMMARY

A method is described which is suitable for studying the migration of polymorphonuclear leukocytes *in vitro*. The migration of leukocytes which have engulfed virulent tubercle bacilli is completely inhibited, whereas a similar effect is not produced by avirulent bacilli taken up by polymorphonuclear leukocytes.

SUMARIO

El Efecto in Vitro de los Bacilos Tuberculosos sobre la Migración de los Fagocitos

La técnica descrita se presta para estudiar la migración de los leucocitos polimorfonucleares *in vitro*. La migración de los que han ingerido bacilos tuberculosos virulentos queda completamente inhibida, en tanto que no producen efecto semejante los bacilos avirulentos absorbidos por los leucocitos polimorfonucleares.

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VIRULENCE AND TUBERCULOGENIC STUDIES OF SIXTY CONSECUTIVE WEEKLY LOTS OF BCG VACCINE PRODUCED BY STANDARD TECHNIQUE[1,2]

KONRAD BIRKHAUG

(Received for publication July 26, 1948)

INTRODUCTION

World-wide acceptance and use of BCG emphasize the significance of methods that insure uniformly safe and potent vaccine preparations. Thus a problem of pressing importance is the development of a standard method for preparing a vaccine that will maintain a high level of viable organisms with stable tuberculogenic, allergenic, and immunizing properties. Of no less importance is the development of a quantitative method that permits periodic assessments of BCG's relative avirulence. Such a method is long overdue since only living vaccine is effective and the chance of a spontaneous enhancement of virulence is still thought of as a possibility by competent and unbiased scientists.

No uniform method for production of BCG vaccine is generally employed today. It is well known that many bacteriologic laboratories make radical alterations in Calmette's original technique (1 to 5). According to Jensen (4) the sole quantitative method which will detect variations in the "virulence" of BCG with some accuracy is a periodic intracutaneous guinea pig test using graded doses of from 0.1 to 0.0001 mg. of BCG vaccine. By these means Jensen was able to detect differences in "virulence" between a stock BCG strain which, contrary to Calmette's technique, had been maintained on Sauton medium from 1927 to 1931, and a new strain received from the Pasteur Institute in Paris in 1931. While the former strain produced frequent nodules with 0.001 mg. and large ones with 0.01 mg., the latter rarely produced nodules with 0.001 mg., and only small ones with 0.01 mg. If the term *virulent* is reserved to indicate organisms which give rise to a rapidly fatal infection or are able to reproduce increasingly in the tissues, it may be questioned whether Jensen's procedure is a proper test with which to determine the virulence of BCG. The reason for this is the fact that the skin lesions produced by these graded doses of microorganisms (dead tubercle bacilli will do the same) are observed for a period of only three weeks after inoculation. Jensen's procedure is an excellent quantitative test of BCG's tuberculogenic potency, the production of a localized and rapidly healing skin lesion, but is hardly a test of virulence.

When the preparation of vaccine was undertaken by the New York State Division of Laboratories and Research in 1946, plans were immediately made to evaluate methods for the preparation and biologic standardization of BCG. The present report describes the methods used and the results of assays made of each lot of vaccine prepared during a twelve month period.

[1] From the Division of Laboratories and Research, New York State Department of Health, Albany, New York.

[2] Presented before Le Premier Congrès International du BCG, Paris, France, June 18–23, 1948.

METHOD OF BCG VACCINE PRODUCTION

Potato cultures: The composition of Calmette's glycerolated bile-potato and water-potato media have not been altered. Two strains of BCG (No. 805. Series 1 and 2) were obtained from the Pasteur Institute in September, 1946. These strains were found to possess identical tuberculogenic, allergenic, and immunizing properties. They have since been transferred every two weeks in a locked laboratory and maintained in a locked incubator in which no other strain of *M. tuberculosis* or other bacteria are kept. Each set consists of one glycerolated-water and one glycerolated-bile potato subculture. The former is the seed from which the film on its liquid portion is transferred to Sauton medium for vaccine production. The glycerolated-bile potato subculture is for attenuation of virulence, according to Calmette's (6) contention, but more practically for restoration of the veil-like film production on glycerolated-water potato cultures which by six to eight successive biweekly passages has a tendency to grow roughly and less luxuriantly than following the first passages. For this purpose, Calmette's original technique has been followed, which consists of interposing one or two biweekly passages of BCG on the glycerolated-bile potato medium every two months. Since film development on the liquid portion of the glycerolated-water potato medium is essential for the seeding of Sauton medium for subsequent vaccine production, it is the practice at present to tilt the one week old glycerolated-water potato culture on the side until the liquid frees the small fragments of the veil-like film along the edges of the potato surface and floats them onto the liquid portion of the medium. This insures a luxuriant supply of film for transfers to Sauton medium the following week.

Sauton cultures: The composition of Sauton medium has not been altered. Ehrlenmeyer flasks (350 ml.) containing 160 ml. of Sauton medium have been used exclusively. The veil-like film in the two week old glycerolated-water potato culture is transferred with a 3 by 1 cm. platinum spatula to the surface of the Sauton medium. At 37.5°C. the film covers about half the surface in three days and the entire surface as well as a few cm. on the sides of the flask in seven days. Such growth within one week is used as the criterion of a normal BCG Sauton I culture. At this time transfers are made with a spiral-shaped platinum wire spade, having a diameter of 25 mm. The film along the border is carefully scooped onto the spade in folded fashion and this is again floated on Sauton medium where it flattens out promptly. One spadeful is sufficient for each Sauton II flask. These cultures grow much more rapidly than Sauton I cultures and the entire surface is usually covered with film in four days. After ten days' growth at 37.5°C., the densely coiled and 3 to 5 mm. thick amber-colored film is harvested for vaccine. This is an alteration in Calmette's original technique which specifies 20 to 25 day old Sauton II culture for vaccine production. The custom in many laboratories is to use 21 to 30 day old Sauton II cultures (2, 7). It was decided to shorten the incubation of the Sauton II cultures to 10 to 11 days when serial Loewenstein cultures revealed that such cultures contained between 20 and 40 million living bacilli per mg. of semidry weight or 80 to 160 million living bacilli per mg. of absolutely dry vaccine while the 3 to 4 week old Sauton II cultures contained approximately one-half that number. The results of vaccination with the 10 to 11 day old Sauton II culture vaccine have been uniformly better, especially with the multiple puncture technique, than with vaccine prepared from the 21 to 30 day old Sauton II cultures.

Semidry and dry weight of BCG in 10 to 11 day old Sauton II Cultures: For the purpose of determining the growth curve of BCG in 10 to 11 day old Sauton II cultures in 160 ml. of medium it has been the practice to single out such a culture once a week for one year for exact determination of the semidry and dry weight. The culture is emptied into a Büchner suction filter supplied with a fine filter paper (Whatman No. 3) which retains the smallest particles of BCG. Suction is continued until no more liquid is expressed from the mass. After the semidry weight is determined, the mass is placed in a dry sterilizer at 100°C. until a constant weight is obtained. By grouping these cultures together into twelve weekly lots for the purpose of statistical analysis, the data presented in table 1 and summarized in figure 2 were obtained.

FIG. 1. One week old Sauton I BCG culture; 10 day old Sauton II BCG culture.

TABLE 1

Weight of BCG in Sauton II Cultures

Statistical analysis of semidry and dry weight (Gm.) of BCG harvested from 160 ml. Sauton medium after 10 to 11 days' incubation at 37.5°C.

(Twelve cultures in each group)

WEEKLY LOTS OF SAUTON II CULTURES	SEMIDRY WEIGHT		DRY WEIGHT		RATIO
	Average	Sigma	Average	Sigma	
1 to 12 weeks	5.971	0.503	1.475	0.089	4.05:1
13 to 24 weeks	5.733	0.421	1.456	0.088	3.94:1
25 to 36 weeks	5.675	0.350	1.480	0.100	3.83:1
37 to 48 weeks	5.669	0.495	1.428	0.084	3.97:1
49 to 60 weeks	5.715	0.339	1.452	0.128	3.94:1

Probability*

WEEKLY GROUP COMPARISONS	*t*	P	*t*	P	
1 to 12 vs. 13 to 24	1.200	0.23	0.134	0.88	
1 to 12 vs. 25 to 36	1.602	0.14	0.034	0.90	
1 to 12 vs. 37 to 48	1.418	0.20	1.278	0.23	
1 to 12 vs. 49 to 60	1.398	0.21	0.654	0.32	

* Significant differences ($P \leq 0.01$) require that $t \geq 2.819$ when each group contains 12 samples (8).

It will be noted that a remarkable stability obtained in the semidry and dry weights throughout the entire 60 week observation period and that not a single significant deviation occurred from the first twelve weekly lots of Sauton II cultures to the final lots (49 to 60 weeks). The ratio between the semidry and dry BCG is almost constantly 4:1. Thus the 20 mg. per ml. BCG vaccine used for transcutaneous vaccination methods actually contains 5 mg. of dry BCG per ml., and the 1.0 mg. per ml. BCG vaccine for intracutaneous inoculation contains 0.25 mg. dry BCG per ml.

An attempt was also made to determine the exact population of living microorganisms per milligram of BCG in every weekly lot of vaccine distributed. This is accomplished by serial dilutions of exactly weighed vaccine and by seeding 1 ml. of each of the 10^{-5}, 10^{-6}, 10^{-7}, and 10^{-8} dilutions on 5 large tubes of Loewenstein's egg medium. This study is still incomplete.

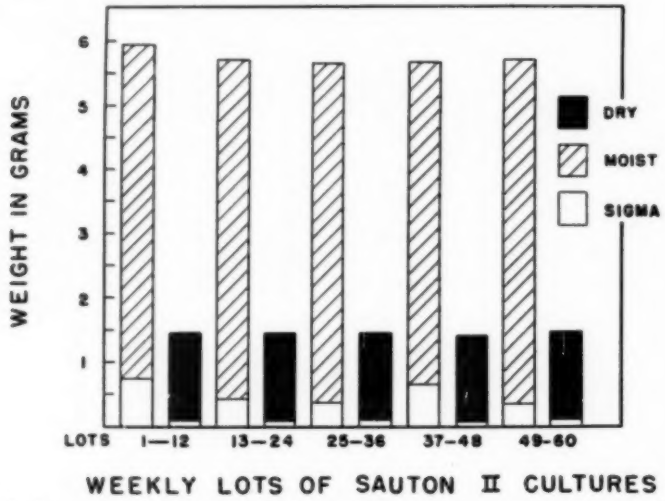

FIG. 2. Average semidry and dry weights of sixty consecutive weekly lots of vaccine produced in 160 ml. Sauton 10 to 11 day old cultures of BCG.

Preparation of vaccine: The traditional Calmette method of harvesting the Sauton II cultures for preparation of vaccine dispenses with the actual weighing of the BCG mass, on the assumption that the 21 to 30 day old 150 ml. Sauton culture contains 5 Gm. semidry BCG. This rule is not absolute and many laboratories desiring a more or less constant concentration of vaccine resort to transferring BCG aseptically to filter paper between which the excess liquid is pressed out. The semidry mass is then weighed in sterile porcelain crucibles after which it is emptied into a flask containing glass or steel balls. In a ball mill the vaccine is mixed with dilution fluid to the proper concentration. To reduce contamination, a harvesting apparatus (figure 3) has been constructed which combines all these operations in a closed system. The slightly agitated Sauton II culture is emptied into a funnel which leads to a cylinder at the bottom of which a strainer filters out the culture. A piston is pressed against the BCG mass within the cylinder until no more liquid is expressed. The shaft of the piston is calibrated and indicates the height of the column of BCG within the cylinder. A nomogram converts height into grams of semidry BCG. The strainer is pushed aside and a quick tap on the handle of the piston releases the column of BCG which drops into a glass cylinder supplied with 1 Kg. of 4 mm. wide and 0.5 Kg. of 3 mm. wide SKF inoxidizable steel balls. Before adding diluent, the ball mill is rotated at 30 r.p.m. for two

to three minutes until the BCG mass has become finely divided into an oily paste and adheres to the sides of the glass cylinder and the steel balls.

The diluent recommended by Calmette is composed of one part of Sauton medium and three parts of distilled water. In order to make the vaccine isotonic and more easily tolerated when injected intracutaneously, physiologic salt solution has been substituted for the distilled water. When the mass of BCG has been sufficiently homogenized, about 10 ml. of diluent are added and the ball mill is rotated for two minutes until a semiliquid paste is formed. Sufficient diluent is then added to make the final concentration of 20 mg. per

FIG. 3. Harvesting and dispensing apparatus for BCG vaccine.

ml. semidry BCG for the transcutaneous methods of vaccination, *i.e.*, to 5.540 Gm. of BCG mass is added 277 ml. of diluent. The ball mill is now rotated at 30 r.p.m. for five minutes. To the glass cylinder on the right in figure 4 is added 5 ml. of the 20 mg. per ml. BCG vaccine (100 mg.) per 95 ml. of diluent in order to make 1.0 mg. per ml. BCG for the intracutaneous method of vaccination. As mentioned before, these concentrations contain 5.0 mg. per ml. and 0.25 mg. per ml. dry BCG respectively.

As shown in figure 4, the vaccine from either glass cylinder is dispensed in 5 and 10 ml. vials by means of a one way suction system that is operated by a foot pedal. By means of this apparatus, one person may fill, stopper, and seal 8 to 10 vials per minute.

Tests for purity of the vaccine: Control tests to rule out the presence of contaminating microorganisms in the vaccine are made by inoculating 0.5 ml. of the fluid portion of the

Sauton II culture, before the film is harvested, into 20 ml. of meat-infusion semisolid medium (*F32B*) (9); 20 ml. of meat-infusion broth, aerobic and anaerobic (*F3B*); and in a pour plate using beef-infusion agar with 0.2 per cent of glucose (*F35A*). These tests are repeated with the 20 mg. per ml. and the 1.0 mg. per ml. vaccines in bulk before dispensing, with the residue after dispensing, and with one vial of each twenty dispensed. A duplicate flask of 100 ml. of the 1.0 mg. per ml. material in bulk is tested simultaneously by a member of the sterility test group of the Antitoxin, Serum, and Vaccine Laboratories. A volume of 160 ml. of meat-infusion semisolid medium (*F32B*) is inoculated with 5 to 5.5 ml. of the material; two aerobic and two anaerobic tubes of meat-infusion broth (*F3B*) with 0.5 ml. each.

If no growth of contaminating microorganisms appears in the various inoculated media after twenty-four hours' incubation, the vaccine is distributed for a period of seven days.

FIG. 4. Dispensing BCG vaccine in vials.

Preliminary studies indicate that the efficacy of the vaccine is not impaired by the addition to the diluent of 20 units of penicillin per ml. of the intracutaneous vaccine. This concentration of penicillin completely inhibits the growth of staphylococci and streptococci during the 10 day period recommended for use of the vaccine before it is returned to the Division of Laboratories and Research. This precaution is taken only with the 1.0 mg. per ml. vaccine because penicillin is completely destroyed by the 20 mg. per ml. vaccine within a few days.

QUANTITATIVE TESTS FOR STABILITY OF BCG'S VIRULENCE

For every lot of BCG vaccine prepared weekly, two tuberculin-negative guinea pigs weighing approximately 350 Gm. are injected subcutaneously in the left hind leg with 0.5 ml. of the 20 mg. per ml. vaccine, or 10 mg. semidry weight of BCG. Tuberculin tests are repeated at monthly intervals. One month after inoculation, 100 per cent positive edematous reactions, which exceed 10 by 10 mm. in

diameter within forty-eight hours, are obtained with 10 mg. of Old Tuberculin. Two months after inoculation, approximately 85 per cent positive edematous reactions are obtained with 0.01 mg. of Old Tuberculin. Six months after inoculation, positive reactions occur in approximately 70 per cent of the animals tested with 0.001 mg. of Old Tuberculin. Throughout the entire six month period, 0.1 mg. Old Tuberculin yields positive reactions in 100 per cent of the animals tested.

Skin puncture through a drop of either living or dead BCG (20 mg. per ml.) results in an accelerated tubercle formation, consisting of erythema, induration and suppuration. This reaction is observed regularly in these animals from three weeks after inoculation until they are killed three and six months after inoculation. The accelerated reaction begins a few hours after the puncture is made, reaches its height in six to ten days, and heals completely within a month. In the normal guinea pig such a puncture slowly leads to a papular development in one week, reaching its height in three weeks when it subsides slowly without any tendency to suppuration. After two months no trace is found of the original lesion, while in the allergic animals a slightly pigmented and sunken area in the skin invariably remains.

The only visible manifestation of the subcutaneous inoculation with BCG is a rapidly developing sterile abscess in the left hind leg. Two weeks after inoculation the leg becomes markedly swollen and the regional lymph nodes are palpably enlarged. One month after inoculation the tumefaction is larger and fluctuation is present. The regional lymph nodes increase in size but remain firm in consistency. Thenceforth the abscess becomes stationary and occasionally breaks down with the discharge of a semisolid caseum rich in acid-fast bacilli. The ruptured abscesses heal promptly but the regional lymph nodes remain hypertrophied and hard.

The weight of animals reflects their apparently normal condition except for the left hind leg abscess and regional lymphadenitis. Table 2 presents the average weights of ten groups, each consisting of 12 inoculated animals. In addition, the weights are recorded of four groups when they were killed three months after inoculation and three groups which were killed six months after inoculation.

It will be noted that none of the groups differed significantly from each other before inoculation and that the same increments in weight had taken place in three and six months, respectively, without any significant deviations between any of the groups. It is apparent, therefore, that the low grade infection with BCG interfered but little with the normal growth of these animals. This fact is confirmed by the 1940 experience (10) in which the growth curve of 24 normal guinea pigs weighing 297 sigma 53.8 Gm. was plotted for 53 preinfection days and 102 days after the intraperitoneal inoculation of 0.0001 mg. (302 viable) human tubercle bacilli. At the end of that period the average body weight at autopsy was 374 sigma 67.3 Gm.

Quantitative assessment of autopsy material: One of each weekly pair of guinea pigs, which had been inoculated subcutaneously in the left hind leg with 10 mg. of BCG, was killed at three and the other at six months after the inoculation.

Autopsy was delayed until the carcass had remained in the refrigerator (2° to 4°C.) for several hours in order to allow the blood to coagulate. This insures uniformity in the quantitative assessment of the volume and weight of various

TABLE 2

Weight of Animals

Statistical analysis of weight (Gm.) of guinea pigs before inoculation with 10 mg. BCG and when killed 3 months (Series A) and 6 months (Series B) afterwards

(Twelve animals in each group)

GROUPS OF ANIMALS	BEFORE INOCULATION			
	Series A		Series B	
	Average	Sigma	Average	Sigma
weeks				
1 to 12	355	28.51	360	29.11
13 to 24	353	33.44	349	40.38
25 to 36	331	37.53	334	39.60
37 to 48	383	58.12	377	38.82
49 to 60	336	42.17	321	53.62

Probability

GROUP COMPARISONS	*t*	P	*t*	P
1 to 12 vs. 13 to 24	0.220	0.82	0.750	0.45
1 to 12 vs. 25 to 36	1.729	0.09	0.686	0.50
1 to 12 vs. 37 to 48	1.446	0.18	0.701	0.48
1 to 12 vs. 49 to 60	0.186	0.85	2.131	0.04

GROUPS OF ANIMALS	3 MONTHS AFTERWARDS		6 MONTHS AFTERWARDS	
	Average	Sigma	Average	Sigma
weeks				
1 to 12	616	68.33	743	63.52
13 to 24	634	69.61	764	62.27
25 to 36	656	53.77	791	84.90
37 to 48	656	83.45	—	—

Probability

GROUP COMPARISONS	*t*	P	*t*	P
1 to 12 vs. 13 to 24	0.588	0.58	0.784	0.46
1 to 12 vs. 25 to 36	1.470	0.15	1.494	0.15
1 to 12 vs. 37 to 48	1.225	0.25	—	—

lymph nodes and organs. The major lymph nodes mentioned in tables 3 and 4 were carefully dissected free from contiguous tissue and their volume determined by water displacement in a specially constructed apparatus (figure 5) with cylinders calibrated to 0.001 ml. The volume of the spleen, liver, and lungs

was determined in the same manner. Finally, the weight of these organs and the pooled lymph nodes was expressed in percentage of the animal's body weight.

TABLE 3

Volume of Lymph Nodes

Statistical analysis of volume (ml.) of lymph nodes in guinea pigs killed 3 months after subcutaneous inoculation in left hind leg with 10 mg. BCG

(Twelve animals in each group)

LYMPH NODES	INOCULATED WITH WEEKLY LOTS OF BCG VACCINE							
	1 to 12 weeks (1)		13 to 24 weeks (2)		25 to 36 weeks (3)		37 to 48 weeks (4)	
	Average	Sigma	Average	Sigma	Average	Sigma	Average	Sigma
Lf. sup. inguinal	0.148	0.071	0.146	0.087	0.157	0.027	0.145	0.091
Rt. sup. inguinal	0.056	0.024	0.051	0.030	0.060	0.024	0.059	0.029
Lf. deep inguinal	0.018	0.011	0.018	0.013	0.018	0.011	0.017	0.012
Rt. deep inguinal	0.007	0.004	0.011	0.006	0.009	0.006	0.008	0.004
Lf. femoral	0.111	0.034	0.110	0.049	0.117	0.053	0.117	0.045
Rt. femoral	0.030	0.028	0.035	0.017	0.028	0.027	0.024	0.017
Periportal	0.010	0.009	0.012	0.014	0.008	0.004	0.007	0.006
Lf. tracheobronchial	0.096	0.055	0.099	0.027	0.093	0.048	0.094	0.062
Rt. tracheobronchial	0.079	0.025	0.078	0.029	0.084	0.038	0.084	0.031
Lf. cervical	0.081	0.014	0.073	0.024	0.080	0.020	0.079	0.021
Rt. cervical	0.079	0.012	0.072	0.017	0.079	0.025	0.082	0.015
Lf. axillary	0.064	0.015	0.066	0.019	0.066	0.014	0.062	0.018
Rt. axillary	0.066	0.022	0.061	0.019	0.066	0.023	0.058	0.018

Probability

LYMPH NODES	(1) vs. (2)		(1) vs. (3)		(1) vs. (4)	
	t	P	*t*	P	*t*	P
Lf. sup. inguinal	0.360	0.68	0.270	0.78	0.086	0.90
Rt. sup. inguinal	0.255	0.81	1.960	0.07	0.262	0.79
Lf. deep inguinal	0.032	0.90	0.027	0.90	0.020	0.90
Rt. deep inguinal	1.960	0.07	0.980	0.38	0.409	0.66
Lf. femoral	0.025	0.90	0.318	0.75	0.357	0.72
Rt. femoral	0.509	0.62	0.173	0.88	0.612	0.32
Periportal	0.377	0.72	0.701	0.49	0.919	0.38
Lf. tracheobronchial	0.016	0.90	0.014	0.89	0.007	0.90
Rt. tracheobronchial	0.009	0.90	0.360	0.72	0.421	0.68
Lf. cervical	1.298	0.23	0.044	0.90	0.046	0.90
Rt. cervical	1.641	0.14	0.049	0.90	0.034	0.90
Lf. axillary	1.347	0.21	1.641	0.14	0.044	0.90
Rt. axillary	0.539	0.59	0.145	0.89	0.051	0.90

By this procedure an attempt was made to assess the degree of hypertrophy caused by the 10 mg. BCG inoculum.

Volume of lymph nodes: The volumetric data on thirteen different lymph

nodes removed from the four groups of animals which were killed three months after inoculation are presented in table 3 and figure 6, and the data for the three

TABLE 4

Volume of Lymph Nodes

Statistical analysis of volume (ml.) of lymph nodes in guinea pigs killed 6 months after subcutaneous inoculation in left hind leg with 10 mg. BCG

(Twelve animals in each group)

LYMPH NODES	INOCULATED WITH WEEKLY LOTS OF BCG VACCINE					
	1 to 12 weeks (1)		13 to 24 weeks (2)		25 to 36 weeks (3)	
	Average	Sigma	Average	Sigma	Average	Sigma
Lf. sup. inguinal	0.155	0.064	0.150	0.069	0.179	0.089
Rt. sup. inguinal	0.051	0.026	0.061	0.029	0.062	0.023
Lf. deep inguinal	0.022	0.014	0.023	0.019	0.025	0.017
Rt. deep inguinal	0.008	0.004	0.010	0.007	0.008	0.004
Lf. femoral	0.105	0.052	0.105	0.048	0.115	0.045
Rt. femoral	0.032	0.014	0.039	0.017	0.040	0.015
Periportal	0.008	0.006	0.010	0.009	0.007	0.002
Lf. tracheobronchial	0.096	0.035	0.093	0.035	0.091	0.060
Rt. tracheobronchial	0.077	0.042	0.086	0.042	0.089	0.039
Lf. cervical	0.073	0.019	0.066	0.016	0.074	0.017
Rt. cervical	0.069	0.018	0.066	0.016	0.076	0.017
Lf. axillary	0.059	0.021	0.061	0.017	0.061	0.010
Rt. axillary	0.064	0.024	0.061	0.021	0.060	0.015

Probability

LYMPH NODES	(1) vs. (2)		(1) vs. (3)	
	t	P	*t*	P
Lf. sup. inguinal	0.145	0.87	0.265	0.79
Rt. sup. inguinal	0.845	0.41	1.036	0.31
Lf. deep inguinal	0.137	0.88	0.270	0.78
Rt. deep inguinal	0.543	0.59	0.019	0.90
Lf. femoral	0.129	0.90	0.480	0.65
Rt. femoral	1.009	0.32	1.398	0.14
Periportal	0.613	0.52	0.980	0.32
Lf. tracheobronchial	0.016	0.90	0.024	0.90
Rt. tracheobronchial	0.502	0.65	0.701	0.49
Lf. cervical	0.044	0.90	0.046	0.90
Rt. cervical	0.042	0.90	1.347	0.21
Lf. axillary	0.049	0.90	0.042	0.90
Rt. axillary	0.058	0.90	0.051	0.90

groups of animals killed six months after inoculation are presented in table 4 and figure 7. It will be noted that the six sets of nodes situated on the left side of the body (inoculated side) are symmetrical with the six sets of nodes on the right

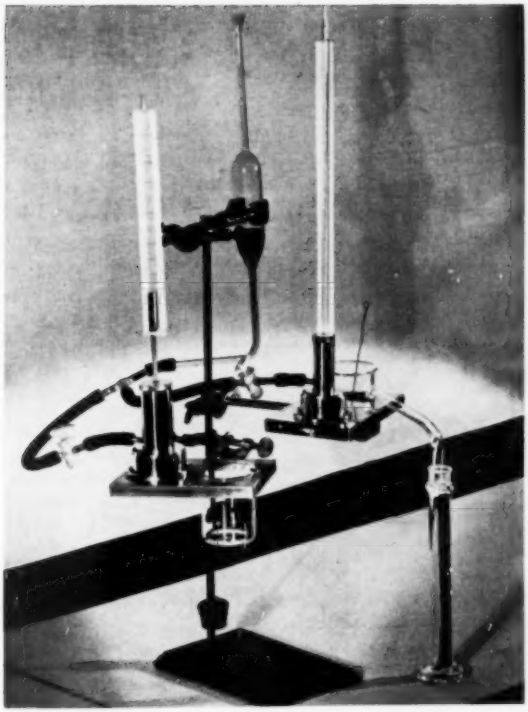

FIG. 5. Volumetric apparatus for measurement of larger organs (left cylinder) and smaller nodes (right cylinder).

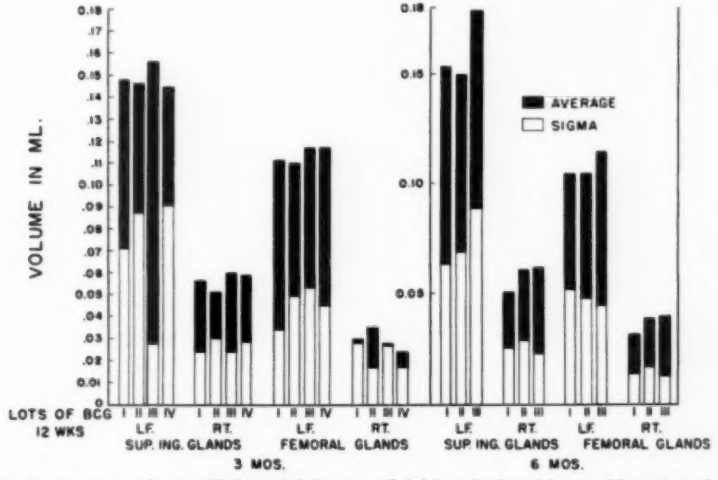

FIG. 6. Average volume of left and right superficial inguinal and femoral lymph nodes in guinea pigs killed three or six months after subcutaneous injection in left hind leg with 10 mg. of sixty consecutive weekly lots of BCG vaccine.

side of the body. Thus the only unpaired lymph node is the periportal node. The measurements of the lymph nodes on the right side may therefore be considered as controls for the lymph nodes on the left side. Thus in tables 3 and 4 it may be seen that the left side superficial and deep inguinal and femoral nodes, which are directly draining the BCG abscess in the left hind leg, are regularly about three times larger in size than the corresponding nodes on the right side of the body. The remaining nodes show no appreciable differences between the left and right sides of the body. It will also be noted in tables 3 and 4 that the hypertrophy of the left superficial and deep inguinal and the femoral nodes pre-

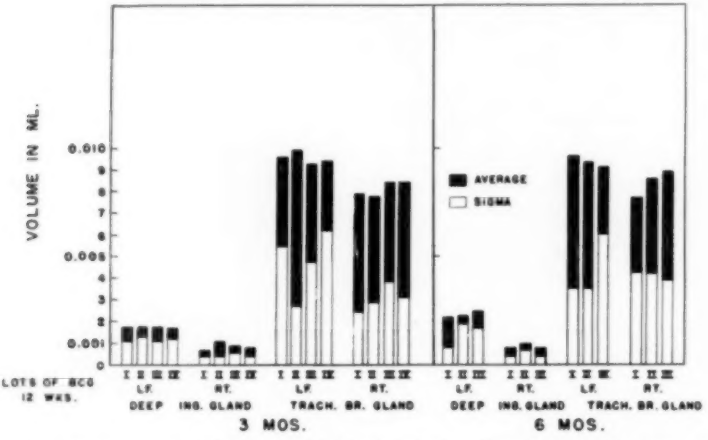

FIG. 7. Average volume of left and right deep inguinal and tracheobronchial lymph nodes in guinea pigs killed three or six months after subcutaneous injection in left hind leg with 10 mg. of sixty consecutive weekly lots of BCG vaccine.

sent no marked increments in size from three to six months after the animals were inoculated with BCG. The frequency of caseum in these nodes was greater three months after inoculation than after six months. Calcified nodes were observed in the reverse order. The frequency of acid-fast bacilli in smears and of colonies in cultures made with caseous material from left superficial and deep inguinal and femoral nodes was greater after three than after six months' inoculation.

The impact on the guinea pig's lymphatic system by a subcutaneous inoculation with 0.1 mg. of virulent human tubercle bacilli (approximately 32,000 viable microorganisms) in the left hind leg, the identical route used with BCG inoculation, is demonstrated by the 1940 experience (11) with 24 control guinea pigs which died from generalized tuberculosis 47 to 51 days later. The volume of the lymph nodes at necropsy was as follows:

LYMPH NODES	VOLUME IN ML.	
	Average	Sigma
Left superficial inguinal	0.570	0.319
Left deep inguinal	0.213	0.217
Left femoral	0.359	0.169
Periportal	0.708	0.352
Left tracheobronchial	0.528	0.265
Right tracheobronchial	0.413	0.209
Left cervical	0.339	0.163
Right cervical	0.323	0.153
Left axillary	0.295	0.191
Right axillary	0.243	0.129

TABLE 5

Weight of Spleen, Liver, Lungs, and Lymph Nodes

Statistical analysis of weight in per cent of body weight of the spleen, liver, lungs, and lymph nodes in guinea pigs killed 3 months after subcutaneous inoculation with 10 mg. BCG

(Twelve animals in each group)

ORGANS	WEEKLY LOTS OF BCG VACCINE							
	1 to 12 weeks (1)		13 to 24 weeks (2)		25 to 36 weeks (3)		37 to 48 weeks (4)	
	Average	Sigma	Average	Sigma	Average	Sigma	Average	Sigma
Spleen	0.101	0.014	0.115	0.020	0.114	0.016	0.122	0.028
Liver	4.708	0.752	4.180	0.595	4.367	0.758	4.639	1.015
Lungs	1.119	0.273	1.079	0.229	0.898	0.176	1.088	0.188
Lymph nodes	0.165	0.045	0.171	0.047	0.160	0.036	0.161	0.062

Probability

ORGANS	(1) vs. (2)		(1) vs. (3)		(1) vs. (4)	
	t	P	t	P	t	P
Spleen	1.906	0.06	1.991	0.06	2.023	0.05
Liver	1.436	0.12	1.058	0.31	0.181	0.85
Lungs	0.372	0.72	2.254	0.04	0.221	0.82
Lymph nodes	0.255	0.81	0.254	0.81	0.172	0.88

Thus it will be noted that the virulent infection produced a generalized lymph node hypertrophy in contrast with the localized process in animals inoculated with 100 times greater dose of BCG, or approximately 400 million viable BCG.

Weight of the spleen, liver, lungs, and lymph nodes: The more exact quantitative data are those expressed in percentage of the body weight of the animal from which the organs were removed since the body weight varies from animal to animal. Table 5 presents such data for the spleen, liver, lungs, and lymph nodes

taken from four groups of animals killed three months after inoculation with BCG. Table 6 shows the data for animals killed six months after inoculation. The results are summarized in figure 8. For comparison, similar data from the above mentioned (11) virulently infected animals are as follows:

ORGANS	PER CENT OF BODY WEIGHT	
	Average	Sigma
Spleen	1.71	1.30
Liver	9.11	1.51
Lungs	3.25	0.81
Total lymph nodes	3.61	0.95

TABLE 6

Weight of Spleen, Liver, Lungs, and Lymph Nodes

Statistical analysis of weight in per cent of body weight of the spleen, liver, lungs, and lymph nodes in guinea pigs killed 6 months after subcutaneous inoculation with 10 mg. BCG

(Twelve animals in each group)

ORGANS	WEEKLY LOTS OF BCG VACCINE					
	1 to 12 weeks (1)		13 to 24 weeks (2)		25 to 36 weeks (3)	
	Average	Sigma	Average	Sigma	Average	Sigma
Spleen	0.099	0.029	0.095	0.015	0.109	0.030
Liver	4.023	0.545	4.216	0.971	4.493	0.607
Lungs	0.846	0.192	0.901	0.226	1.007	0.229
Lymph nodes	0.136	0.040	0.137	0.030	0.164	0.026

Probability

ORGANS	(1) vs. (2)		(1) vs. (3)	
	t	P	*t*	P
Spleen	0.409	0.65	0.791	0.42
Liver	0.573	0.58	1.568	0.14
Lungs	0.612	0.54	1.499	0.15
Lymph nodes	0.066	0.90	1.960	0.06

Table 5 shows that the weight of the spleen in the animals killed three months after inoculation with BCG varied between 0.101 and 0.122 per cent of the animals' body weight. The weight varied between 0.095 and 0.109 per cent of the animals' body weight at six months after inoculation (table 6). At no time was any significant deviation observed between any two groups in these series. Of greater importance is the fact that no macroscopic tubercle was ever found in the spleen of these animals.

The weight of the liver (tables 5 and 6) varied between 4.023 and 4.708 per cent of the animals' body weight three and six months after inoculation; the

lungs between 0.898 and 1.119 per cent of the animals' body weight; and finally, the total lymph nodes between 0.136 and 0.171 per cent. With the exceptions of the fibrocaseous hypertrophy observed in the left superficial and deep left inguinal nodes and the left femoral nodes adjacent to the BCG inoculation abscess, no macroscopic tuberculous lesions were seen in the liver and lungs of the animals killed three and six months respectively after inoculation with BCG from 48 different lots of vaccine prepared during one year.

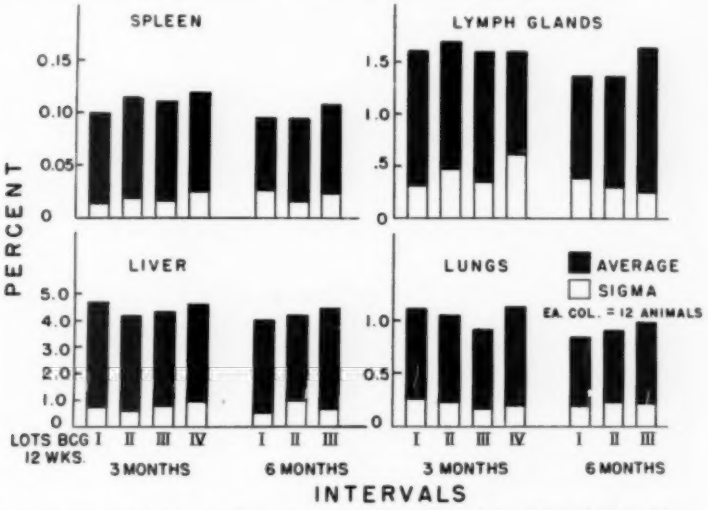

FIG. 8. Average weight of spleen, liver, lungs, and total lymph nodes in guinea pigs killed three or six months after subcutaneous injection in left hind leg with 10 mg. of sixty consecutive weekly lots of BCG vaccine.

Comment

The data on the lymph nodes, spleen, liver, and lungs indicate that the avirulence of BCG is not absolute and that the very low grade virulence of BCG is of a significantly stationary type for vaccine prepared by the method set forth in this presentation. There can be no question about the reliability of this quantitative procedure to detect significant deviations in BCG's virulence should such ever take place. It would seem desirable, therefore, that some such quantitative assessment of lesions produced in guinea pigs by each lot of vaccine prepared for use in man should become a standard procedure in order that laboratories entrusted with the production of vaccine at all times may be prepared to report objectively on the avirulence of their preparations.

BCG'S TUBERCULOGENIC POTENCY IN ANIMAL SKIN TESTS

Following Jensen's (4) study on variations in the "virulence" of different strains of BCG cultivated by different methods, it was decided from the very

start of the present investigation to evaluate the tuberculogenic potency of every lot of vaccine for one year. In an attempt to increase the objectivity of the investigation as much as possible, most of the observed data were reduced to measurements of the local skin lesion at one and three week intervals after inoculation. For this purpose a white tuberculin-negative guinea pig, weighing between 300 and 350 Gm. was used. The skin on the abdomen and the left side of the body was depilated and thereafter washed with alcohol and ether. Intracutaneous injections of 0.1 ml. of saline dilutions of the BCG vaccine containing 1.0 mg., 0.1 mg., 0.01 mg., and 0.001 mg. of vaccine (final 0.1, 0.01,

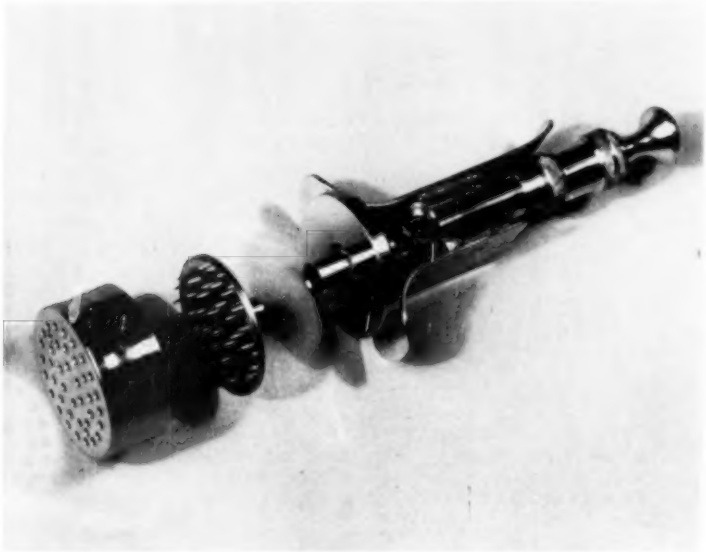

FIG. 9. Spring-actuated multiple puncture apparatus with detachable needle holder and head plate for individual BCG vaccination.

0.001, and 0.0001 mg.) were made in the four quadrants of the abdomen. Care was taken to inject the vaccine as superficially as possible so that a white bleb remained visible for about five minutes. Three to five drops of the transcutaneous (20 mg. per ml.) vaccine were spread evenly across the depilated skin on the left side of the body. Holding the skin taut, forty punctures, approximately 3 mm. in depth, were made through the skin with the automatic multiple apparatus (12) (figure 9). The skin was stretched slightly in order to verify the presence of petechial bleeding from each puncture. One or two drops of the vaccine were then spread across the punctured area and the animal replaced in its cage.

Typical vaccination nodules with suppurating centers were produced regularly with 0.1 and 0.01 mg. of BCG vaccine and only a hardened nodule with 0.001

mg. No lesion was produced by 0.0001 mg. of the vaccine. After one week, the multiple puncture sites presented approximately 1.5 mm. wide red, raised, and firm papules. These measured approximately 2.6 mm. in width and 1.5 mm. in height after three weeks. Desquamation and healing occurred after four weeks and were complete three to four weeks later. Suppuration in individual papules was exceedingly rare. For statistical analysis, readings of the intracutaneous and transcutaneous lesions were most advantageously made one and three weeks after inoculation. At the latter time the maximum development was reached. Tables 7 and 8 present the data on 60 individual guinea

TABLE 7

BCG Skin Lesions

Statistical analysis of maximum diameter (mm.) of skin lesions produced in guinea pigs one week after intracutaneous and transcutaneous inoculations with graded doses of BCG

(Twelve animals in each group)

WEEKLY LOTS OF BCG VACCINE	INTRACUTANEOUS INJECTION						MULTIPLE PUNCTURE	
	0.1 mg.		0.01 mg.		0.001 mg.		20 mg./ml.	
	Average	Sigma	Average	Sigma	Average	Sigma	Average	Sigma
1 to 12 weeks	5.75	0.59	4.33	0.74	2.33	0.62	1.63	0.22
13 to 24 weeks	5.42	0.49	3.83	0.79	2.25	0.43	1.54	0.13
25 to 36 weeks	5.67	0.65	4.09	0.64	2.33	0.62	1.54	0.28
37 to 48 weeks	6.13	0.49	4.33	0.62	2.75	0.43	1.75	0.33
49 to 60 weeks	6.50	0.50	4.59	0.76	2.67	0.47	1.88	0.69

Probability

COMPARISON OF WEEKLY GROUPS	*t*	P	*t*	P	*t*	P	*t*	P
1 to 12 vs. 13 to 24	1.416	0.18	1.512	0.15	0.754	0.48	1.161	0.28
1 to 12 vs. 25 to 36	0.029	0.90	0.806	0.41	1.592	0.15	0.848	0.41
1 to 12 vs. 37 to 48	1.634	0.12	1.764	0.11	1.838	0.08	1.014	0.29
1 to 12 vs. 49 to 60	0.316	0.78	0.931	0.32	1.470	0.18	2.663	0.02

pigs, which for statistical purposes have been subdivided into groups of 12 animals, each of which was inoculated with successive lots of vaccine prepared at weekly intervals during sixty weeks. These data are summarized in figure 10.

Comment

One is struck by the relative stability of the skin reactions produced by each graded dose of BCG vaccine both after one week and three weeks, whether tested by the intracutaneous or transcutaneous routes. In table 7 it would appear that the 0.1 mg. dose of BCG grew more tuberculogenic from the first one to 12 weekly lots, which produced a 5.75 sigma 0.59 mm. wide suppurating infiltration in the skin, until the final 49 to 60 weekly lots which produced 6.50 sigma 0.50 mm. similar lesions. The multiple puncture lesions produced by the same lots of

TABLE 8

BCG Skin Lesions

Statistical analysis of maximum diameter (mm.) of skin lesions produced in guinea pigs three weeks after intracutaneous and transcutaneous inoculations with graded doses of BCG

(Twelve animals in each group)

WEEKLY LOTS OF BCG VACCINE	INTRACUTANEOUS INJECTION						MULTIPLE PUNCTURE	
	0.1 mg.		0.01 mg.		0.001 mg.		20 mg./ml.	
	Average	Sigma	Average	Sigma	Average	Sigma	Average	Sigma
1 to 12 weeks	6.92	0.76	5.17	0.80	3.42	0.45	2.75	0.25
13 to 24 weeks	7.09	0.82	5.25	0.60	3.09	0.42	2.38	0.46
25 to 36 weeks	6.92	0.64	5.75	0.60	3.42	0.47	2.42	0.34
37 to 48 weeks	7.25	0.44	5.67	0.49	3.67	0.74	2.59	0.34
49 to 60 weeks	7.17	0.38	5.92	0.36	3.59	0.39	2.79	0.38
Probability								
COMPARISON OF WEEKLY GROUPS	*t*	P	*t*	P	*t*	P	*t*	P
1 to 12 vs. 13 to 24	0.502	0.61	0.264	0.79	1.795	0.09	2.322	0.04
1 to 12 vs. 25 to 36	1.568	0.15	1.920	0.07	1.176	0.28	0.760	0.48
1 to 12 vs. 37 to 48	1.245	0.23	1.749	0.09	0.943	0.32	1.223	0.22
1 to 12 vs. 49 to 60	0.973	0.35	*2.824*	*0.01*	0 946	0.37	0.279	0.79

Significant deviation italicized.

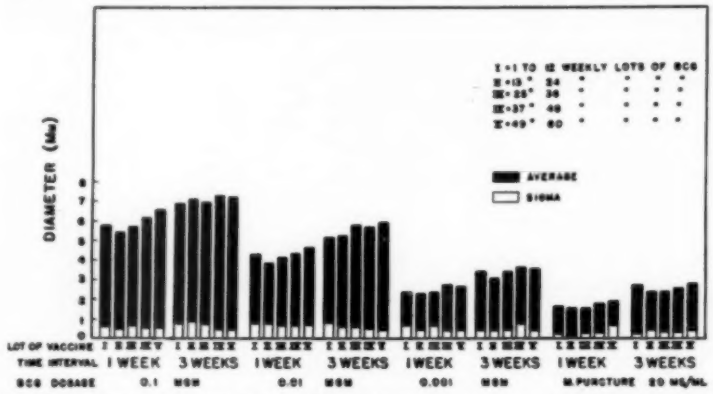

FIG. 10. Average diameter of skin lesions in guinea pigs one and three weeks after intracutaneous or transcutaneous (multiple puncture) inoculations with graded doses of sixty consecutive weekly lots of BCG vaccine.

vaccine appear to show the same trend. But only in the latter case did the deviation between the first and last weekly lots approach significance. That an assumption of increased tuberculogenic potency in the vaccine toward the end of the first year's cultivation is unfounded becomes clear by the data presented

in table 8 where the maximum skin lesions with the variously graded doses of vaccine have become remarkably stationary. The sole exception is the significant deviation in the 49 to 60 weekly lots of 0.01 mg. But this instance is not substantiated in the lesions produced by the 0.1 mg. and 0.001 mg. of the vaccine. Thus it may be concluded that the tuberculogenic potency of BCG is relatively stable for the BCG vaccine which is prepared by the standardized method. It should also be added that the tuberculin reactions, observed in these animals with graded doses of Old Tuberculin ranging from 10 to 0.001 mg., bring out the fact that the degree of tuberculin hypersensitiveness showed the same stability throughout the study. An area of induration exceeding 10 by 10 by 1.5 mm. forty-eight hours after intracutaneous injection of graded doses of tuberculin occurred as follows: one week after inoculation, approximately 150 mm.^{3} with 10 mg. OT; at two weeks, 390 mm.^{3} with 1.0 mg. OT; three weeks, 510 mm.^{3} with 0.1 mg. OT. Thereafter, until the animals were killed three and six months later, a reaction of approximately 200 mm.^{3} induration uniformly occurred with 0.01 mg. OT.

BCG'S TUBERCULOGENIC AND ALLERGENIC POTENCY IN MAN

Since January, 1947, more than 2,000 tuberculin-negative persons, with no evidence in the chest roentgenograms of disease of the lungs, have been vaccinated with the same lots of BCG vaccine. The multiple puncture method has been used except in a dozen persons injected intracutaneously with 0.1 mg. BCG. The vaccine was invariably used within one week after its preparation.

A 4 by 4 cm. piece of thin paper, sterilized for fifteen minutes at 100°C., was moistened on both sides with the 20 mg. per ml. BCG vaccine in a sterile Petri dish and placed on the ether-cleansed skin. The skin was held taut by grasping the arm or thigh on opposite sides, the head plate evenly pressed against the paper and the trigger pushed. As the needle plate descends the forty needle points become coated with vaccine and carry it into the epidermis to a depth of 1 to 3 mm. The paper is removed after one or two minutes. No bandage is necessary. Pin-point bleeding may be seen in the punctures when the skin is stretched. Excessive spontaneous bleedings should be avoided; and can be readily controlled by adjusting the extension of the needles to 2 or 3 mm. beyond the head plate. Between each vaccination, the apparatus is disinfected by immersing the head plate with the needle points protruding in boiling water from 10 to 20 seconds, followed by 10 to 15 seconds in cold sterile water. The apparatus is then placed on a pad of sterile absorbent cotton to remove excess water. A new model of the apparatus has a detachable head plate and needle plate which can be replaced with sterile parts for every vaccination. The multiple puncture vaccination causes no untoward reaction and necessitates no special care. After a few days, the skin regains its normal appearance. Suppuration of the regional lymph nodes does not occur. Within ten to twenty days the local puncture marks reappear as inflamed and infiltrated papules 2 to 3 mm. wide. These lesions cause no general symptoms. Very rarely do they become enlarged. The reactions disappear in a few weeks, and from two to three months after vaccination the process is completely resorbed without residual marks or scars. Only occasionally, faint white dots may be observed. The tuberculin test with 1.0 mg. Old Tuberculin becomes positive in nearly 100 per cent of successfully vaccinated persons 8 to 12 weeks after vaccination if visible papules have been present. A reaction is considered positive when definite induration or edema of at least 6 to 8 mm. diameter, regardless of whether redness is present or not, is present forty-eight to seventy-two hours after injection.

In the author's series of about 500 multiple puncture vaccinations between January, 1947 and May, 1948, a remarkable uniformity of the local reactions has been observed with the various lots of vaccine. Although the local reactions may be variable within one group of vaccinated persons, doubtlessly due to variations in the skin and the depth of the punctures, no really severe local reactions have been encountered. The rare instances of suppuration in individual papules have usually been associated with questionable positive-tuberculin reactors at the time of vaccination, who subsequently have presented an accelerated papular reaction (13–15).

It is too early to present data on the persistence of tuberculin hypersensitiveness in these persons. A group of 20 employees of the Division, who were vaccinated between ten and seventeen months ago, were simultaneously retested recently with 0.1 mg. OT and 0.0002 mg. PPD on the flexor surface of the left forearm. Two days later 100 per cent gave positive reactions with OT (varying between 10 by 10 and 25 by 25 mm. of induration) and only 56 per cent gave positive reactions with PPD (varying between 6 by 6 and 16 by 16 mm. induration). The same discrepancy was observed in 31 nurses who were retested with the same doses of OT and PPD one month after successful multiple puncture vaccination. After forty-eight hours 93.3 per cent gave positive reaction with OT and only 26.7 per cent with PPD, the former reactions varying between 6 by 6 and 18 by 18 mm., and the latter between 6 by 6 and 10 by 10 mm. of induration. Similar observations have been made by other physicians in New York who have also noted that, whereas the reactions with OT in BCG vaccinated persons are sharply raised, markedly edematous, and usually of two and three plus intensity, the reactions with PPD are usually flat and poorly demarcated and only slightly indurated.

Such problems as the best tuberculin test material to detect tuberculin hypersensitiveness in BCG vaccinated persons, the best method of vaccination to produce the most lasting tuberculin hypersensitiveness, and the usefulness of lyophilized BCG vaccine deserve particular consideration at present. But the subject of primary importance which this First International BCG Congress should consider is the need for a uniform technique for the production of vaccine and periodic control of its avirulence and tuberculogenic potency by exact quantitative procedures. The need for an international standard technique is very real.

SUMMARY

Uniform methods are presented for the continuous production at weekly intervals of a relatively stable and effective BCG vaccine and for periodic control of its avirulence and tuberculogenic properties.

A series of sixty consecutive weekly lots of BCG vaccine produced by such methods has been assessed quantitatively for invasiveness and the production of tissue hyperplasia in guinea pigs sacrificed three and six months, respectively, after inoculation. The data confirm that BCG's avirulence is not absolute, but is of a significantly low and stationary degree to render the animals tuberculin hypersensitive.

The same lots of vaccine have been assayed for their tuberculogenic properties, their ability to produce localized intracutaneous and transcutaneous skin lesions. The data indicate that this potency is significantly stable when the vaccine is prepared by the methods employed in this study.

Experience on more than 2,000 persons vaccinated with the material from these sixty consecutive weekly lots of BCG vaccine confirm the stability of BCG's tuberculogenic potency and relative avirulence.

An international standard technique for the preparation of BCG vaccine and for the periodic control of its avirulence and tuberculogenic potency is recommended.

SUMARIO

Estudios de la Virulencia y Tuberculogenia de Sesenta Lotes Semanales Consecutivos de Vacuna BCG Producida Conforme a una Técnica Establecida

Descríbense técnicas uniformes para la continua producción semanal de una vacuna BCG relativamente estable y eficaz y para la comprobación periódica de su avirulencia y propiedades tuberculógenas.

Una serie de 60 lotes semanales consecutivos de vacuna BCG producida con dichas técnicas fué justipreciada cuantitativamente en cuanto a facultad invasora y producción de histohiperplasia en cobayos sacrificados a los tres y seis meses, respectivamente, de la inoculación. Los datos acopiados confirman que la avirulencia de BCG no es absoluta, pero sí significativamente baja y estacionaria para convertir a los animales en hipersensibles a la tuberculina.

Los mismos lotes de vacuna fueron valorados con respecto a sus propiedades tuberculógenas, o sea su capacidad para producir lesiones intra y transcutáneas localizadas. Los datos obtenidos indican que esta potencia es significativamente estable cuando se prepara la vacuna por las técnicas empleadas en este estudio.

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A SANATORIUM PROGRAM FOR THE BACTERIOLOGICAL DIAGNOSIS OF TUBERCULOSIS[1]

The Results Obtained in Cases Admitted during a Period of Ten Years

C. RICHARD SMITH

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INTRODUCTION

In 1928, Pinner and Werner (1) pointed out that with persistent use of the available methods of sputum examination, "positive" results could be found in an extraordinarily high proportion of cases of clinically active tuberculosis. They found acid-fast bacilli in 99.2 per cent of 507 patients with active disease. They concluded that bacteriological diagnosis of active tuberculosis "... is equal to any diagnostic laboratory procedure and second to none." With the repeated use of culture and guinea pig inoculation of sputum and stomach contents, Decker, Ordway and Medlar (2) found bacilli in 67 out of 97 patients with clinically active, minimal pulmonary tuberculosis.

Diagnostic Standards, 1940 (3) includes this statement: "If sputa and gastric washings are carefully and repeatedly examined... negative results are of distinct diagnostic value. It can be safely said that a patient with demonstrable parenchymal infiltration in the lung that is apparently active, in whom tubercle bacilli cannot be demonstrated, probably has a nontuberculous pulmonary lesion." Willis and Kelly (4) investigated the value of examining the expectoration of several days pooled together. In a series of cultures, 63 per cent of all "positives" were obtained from one day specimens and 92 per cent from ten day specimens. In comparing the results from examination of two successive seven day specimens, using concentration and culture, they found that the first would fail by only 7.8 per cent to yield as many "positives" as both specimens. Their recommendation was the collection and examination of a week's total of sputum.

In 1942 the Committee on Standard Laboratory Procedure of the American Trudeau Society recommended a program for bacteriological diagnosis (5) as follows:

1. Direct smear of a morning specimen and a specimen collected over a period of twenty-four hours, or as long a time as the circumstances require. (The direct smear may be omitted if the operator chooses to do a concentration.)
2. If the direct smear is negative, concentrate the same sputum specimen.
3. Culture the same specimens after concentration if the concentration is negative, if less than 5 bacilli are found in the smear, or if there is any possible doubt whether the acid-fast bacilli are true tubercle bacilli.
4. If the first specimen is negative on microscopic examination, repeat the whole procedure on two subsequent occasions.
5. If sputum is not obtainable, gastric lavage should be performed and the sediment examined by direct smear, culture, and animal inoculation.
6. A gastric lavage is recommended in patients having little sputum or if the specimens continue to be negative.

[1] From the Barlow Sanatorium, Los Angeles, California.

In a review of bacteriological findings on 2,248 consecutive admissions at Muirdale Sanatorium, Sanford (6) stated that in active reinfection tuberculosis direct smear and concentration tests showed an accuracy of 80 per cent. But, when cultures were also used, "only slightly less than 1 per cent of all paitents with X-ray evidence of activity could not be proved positive."

Bacteriological Program at Barlow Sanatorium

Since 1935 an attempt has been made at Barlow Sanatorium to develop a feasible program of bacteriological examinations that would yield the highest possible proportion of dependable diagnoses. While this program has changed through the years, it was developed to sufficient degree by the summer of 1936 to make it possible to present at this time the results for a period of operation of ten years, from August 31, 1936 to September 1, 1946. At the beginning of the ten year period a twenty-four hour specimen of sputum collected immediately after the patient's admission was examined by direct smear. If "negative," all of the sputum for three days was collected and examined simultaneously by concentration and culture. If the results continued "negative," the three day concentration and culture test was repeated on three separate occasions during the first month of residence and once each in the second and third months. In the second months of residence the stomach contents were aspirated and examined by culture and animal inoculation.

During the ten year period, the examination program for cases remaining "negative" became more intensive. The amount of the specimen was increased until all the sputum expectorated in six days was collected for each set of tests. The number of six day specimens was increased to the point where the sputum was collected for examination almost continuously during the first three months of residence. The number of gastric aspirations was increased to 2 and then to 3 during the first three months, one in each month. In one period all the sputum expectorated for thirty days was collected in six day batches and tested simultaneously by concentration, culture, and animal inoculation. A later development was the pooling of a six day sputum specimen with the aspirated fasting stomach contents for examination by culture and animal inoculation. The evolution of the testing program is outlined in table 1. There have been variations. This represents the average. It will be noted that from February, 1939 on, one-half to two-thirds of all the sputum expectorated during the first three months was examined.

The present program, in operation since January, 1944.

1. Immediately after admission, a twenty-four hour specimen of sputum is collected and examined by direct smear and culture[2, 3].

[2] Culture for identification purposes in case the direct smear is positive for acid-fast bacilli.

[3] A variation is the immediate collection of a forty-eight hour specimen to be examined by direct smear, concentration, and culture.

2. If the direct smear is negative for acid-fast bacilli, a six day specimen is collected and examined by concentration and culture.

3. If the concentration test shows no acid-fast bacilli, the stomach contents plus a second six day specimen are examined by culture and animal inoculation. With minimal lesions or in cases where the diagnosis of tuberculosis is particularly in question, the stomach contents are examined as soon as possible, combined with the first six day sputum specimen.

TABLE 1

Evolution of the Bacteriological Diagnostic Program 1936 to 1946

Tests carried out routinely during the first three months of residence in cases remaining "negative"

PERIOD	SPUTUM TESTS*					GASTRIC CONTENTS BY CULTURE AND GUINEA PIG
	Number			Number of days' expectoration per test	Total days' expectoration examined	
	Concentration and culture	Concentration, culture and guinea pig	Culture and guinea pig†			
8-31-36 to 10-31-37	6			3	18	1
11- 1-37 to 1-31-39	5	1		3	18	1
2- 1-39 to 9-30-40	4	7		6	66	2
10- 1-40 to 7- 1-43	4 to 8	3		6	42 to 66	3
7- 1-43 to 1- 1-44	4 to 8		3	6	42 to 66	3
1- 1-44 to 9- 1-46	7 to 9		3	6	60 to 72	3

* The initial direct smear on a twenty-four hour specimen done in every case is not tabulated.

† These sputums were pooled and examined together with the specimens of gastric contents shown in the last column.

4. If the examinations continue to be negative, six day sputum specimens are collected continuously during the first three months of residence and examined by concentration and culture. Practically, this works out at about one specimen a week.

5. Once each month during the first three months, the aspirated stomach contents are combined with one of the six day sputums for culture and animal inoculation.

When patients continuing in residence for more than three months are still "negative," a four day sputum specimen is collected in each calendar month and examined alternately by concentration and culture and by culture only. Each third month, or oftener, gastric lavage is performed and the material, after being pooled with a four day sputum specimen, is cultured and injected into animals. In addition, search for other pathogenic microorganisms, especially fungi, is carried out.

As a general proposition, in cases once proved positive, the simplest test capable of demonstrating the bacilli is performed in each calendar month.

Notes on Technique

Collection: Sputum specimens are collected in quarter-pint, paraffin-impregnated, heavy paper containers with tight fitting covers[4]. These containers have wide mouths; they do not upset easily; they will not wet through in several days; and when the cover is in place they will not spill. They are used only once, then discarded. They are assumed to be sterile as far as tubercle bacilli are concerned. Multiple day specimens are collected two days at a time in separate containers, each container being immediately refrigerated and the portions being pooled on the morning of the test. A mimeographed sheet is sent to each new patient explaining the mechanism of raising and expectorating sputum and including directions for collection of specimens. Sometimes it is necessary for a nurse, technician or doctor to explain this personally to the patient. Each patient is required to provide a specimen of either sputum or saliva obtained by coughing or clearing the throat because some patients will deny the existence of sputum for aesthetic reasons and some are unconscious of its presence. Patients who send large amounts of saliva or sinus drainage are asked to expectorate only pulmonary sputum into their collection container while discharging excess saliva and mucous into the regular disposal cup.

Microscopic tests: Direct and concentration smears are all examined ten minutes or until found "positive." When fewer than 7 bacilli are found, a confirming test on another specimen is required for a bacteriological diagnosis.

Concentration tests are carried out by means of a flotation technique (7). Briefly, the sputum is homogenized by vigorous shaking with an equal amount of 0.5 per cent sodium hydroxide, diluted 1:10 with water and shaken again with 1 cc. of xylol. Smears are prepared from the floated surface layer that develops on standing. A picric acid counter stain is used.

In order to avoid the possibility of false positive reports due to the presence of dead bacilli from a previous test, the glassware is baked at 250° C., a temperature high enough to carbonize organic matter, or treated with sufficiently strong cleaning acid to destroy the bacillary bodies.

Concentration tests are always accompanied by culture, carried out simultaneously on the same specimen after homogenization.

Culture: The sputum-sodium hydroxide digest, prepared as above, is mixed with an equal amount of 2.5 per cent oxalic acid, centrifuged, and the sediment planted on 2 tubes of Petragnani's medium[5], 2 drops to a tube (8). The culture tubes are discarded at two months.

Animal inoculation: The sputum-sodium hydroxide digest, as above, is washed once and the sediment inoculated subcutaneously into the lower flank of a guinea pig. Animals with clinical signs of disease are autopsied at one month, others at two months. Visceral disease and the demonstration of acid-fast bacilli are required for the report of a positive test (10).

Gastric tests: Fasting stomach contents and washings with or without added sputum are made up to a final concentration of 0.5 per cent sodium hydroxide (by addition of 4 per cent sodium hydroxide in the amount of 1/8 the volume of the specimen), shaken, and the sediment divided for culture and animal inoculation as above (10). Four tubes of culture medium are planted with sediment from the sodium hydroxide digest, an equal number with that from the oxalic acid-treated material. (In cases where the culture is positive and the guinea pig negative, the cultural growth is inoculated to prove its virulence.)

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[4] "White-tite" containers manufactured by Fibre Board Products, Inc., Stockton, California; or "Seal-Right" containers manufactured by Seal Rite, Inc., Fulton, New York.

[5] Actually at present, 2 tubes of Lowenstein's (Jensen modification), 2 of yolk-potato medium, as recommended by the Committee on Laboratory Procedure of the American Trudeau Society (9), and 2 of Petragnani's medium.

Microscopic examinations are never done on stomach contents since, although the stomach tubes and other equipment are sterilized, dead tubercle bacilli from a previously positive case may adhere to the tube or syringe and give a microscopically false positive result.

Clinical Evaluations

The clinical evaluation of each case was considered by the clinical staff headed by Dr. Howard W. Bosworth, including interpretations of the roentgenograms by Dr. Rolla G. Karshner, and final designations by Dr. Franklin S. Reding. The cases were classified[6] as to the presence of activity and according to the stage of the disease. Active disease was diagnosed when the admission roentgenogram showed characteristic soft shadows and when successive pictures over a period of months or years showed unquestioned changes. The presence of signs and symptoms not explained by other conditions was given due weight. Finally, and possibly at variance with other clinicians, all cases bacteriologically positive were considered "active." This was so even in those positive only by culture and animal inoculation.

TABLE 2

Clinical Classification

Patients admitted from August 31, 1936 to September 1, 1946

CLASSIFICATION	ALL ADMISSIONS		PATIENTS RESIDENT TWO MONTHS OR MORE	
	Number	Per cent of total	Number	Per cent of total
Minimal	172	24.2	166	25.6
Moderately advanced	297	41.7	277	42.9
Far advanced	129	18.1	126	19.4
Pleural tuberculosis*	12	1.7	10†	1.5
No active tuberculosis	45	6.3	38	5.8
No tuberculosis	56	7.9	31	4.8
No diagnosis, no treatment	1	0.1		
Total	712	100.0	648	100.0

* No pulmonary tuberculosis demonstrated.

† One case subsequently shown to be neoplastic in origin.

RESULTS

During the ten year period from August 31, 1936 to September 1, 1946, 712 patients were admitted to Barlow Sanatorium. Of these, 648 remained two months or more. The numbers and percentages of the different clinical categories are shown in table 2.

Table 3 shows the numbers and percentages of cases found bacteriologically positive, according to the clinical designation, for those resident two months or more. Of the 569 cases classified as active pulmonary tuberculosis, pulmonary

[6] According to Diagnostic Standards, 1940, National Tuberculosis Association.

secretions were "positive" in 97.4 per cent. Including pleural fluid examinations, bacteriological diagnoses were obtained in 97.7 per cent. Positive results were obtained in 94.6 per cent of cases of minimal tuberculosis.

Of the "positive" cases recorded in table 3, there were 13 positive by one test only: direct smear (Gaffky III) in one case, culture in 4 and animal inoculation in 8. There were 18 cases positive by microscopic tests only: all were Gaffky II or better; in 17 there were 2 or more positive tests; in 16 there were 2 or more tests of Gaffky III or better. In no case was a positive diagnosis dependent on a plus one[7] or a Gaffky I microscopic reading. In only one case was a bacteriological diagnosis made from the concentration test alone. Here there were 6 positive tests varying from plus one to plus four.[8]

TABLE 3

Bacteriological Diagnoses

Patients admitted from 8-31-36 to 9-1-46 who were resident two months or more

CLINICAL CLASSIFICATION	NUMBER OF PATIENTS	BACTERIOLOGICALLY POSITIVE	
		Number	Per cent
Minimal	166	157	94.6
Moderately advanced	277	272*	98.2*
Far advanced	126	125†	99.2†
Pleural effusion, no demon. pulmonary tuberculosis	10	2	20.0
No active tuberculosis	38	0	0
No tuberculosis	31	0	0
Total	648	556	85.8
Total active pulmonary tuberculosis	569	554‡	97.4‡

* 273 and 98.5 per cent including 1 case with "negative" sputum but "positive" pleural fluid.

† 126 and 100 per cent including 1 case in which the pleural fluid was "positive."

‡ 556 and 97.7 per cent including 2 cases with "positive" pleural fluid.

Patients bacteriologically negative with clinically active pulmonary tuberculosis: Among those resident two months or more there were 15 such cases. Eight had minimal; 6, moderately advanced and 1, far advanced tuberculosis. Pertinent data for each case are shown in table 4.

It will be noted that in 2 cases artificial pneumothorax had been instituted before admission. Although the pulmonary disease was undoubtedly active in one and probably active in the other, access to drainage was apparently blocked. But in both cases tubercle bacilli were found in the pleural fluid and, in a sense, a positive bacteriological diagnosis could be made.

In a third case lobectomy had been performed prior to admission. Here a clinical diagnosis of minimal tuberculosis was made on the theory that nondemonstrable active disease must exist in the other lobes.

Of the remaining 12 "negative" cases, clinical review indicated 3 to be un-

[7] One to 6 acid-fast bacilli in ten minutes search.

[8] More than 2 bacilli per field.

questionably "active," *all* with *minimal* lesions. One of these had had rest in bed for eight weeks, and another for twelve weeks, before admission. In the experience of the staff this sometimes is sufficient to result in "closure" of the lesion though not sufficient to allow for complete healing. Among 6 cases rated as probably "active," 4 had had rest in bed for eight weeks or more prior to admission.

TABLE 4

Cases Clinically Active and Bacteriologically Negative

Resident two months or more

CASE	CLINICAL CLASSIFICATION	MANTOUX	PLEURAL FLUID	TREATMENT BEFORE ADMISSION		CLINICAL ACTIVITY REASSESSMENT
				Weeks in bed	Surgical	
1	MA	Positive		8		Probable
2	Min.	Positive				Probable
3	Min.	Positive		10		Probable
4	Min.	Not done	Yes	1	Lobectomy	Questionable
5	Min.	Positive		8		Unquestionable
6	Min.	Positive				Probable
7	MA	Positive		1		Question as to tuberculosis
8	MA	Positive		8		Probable
9	Min.	Positive		3		Unquestionable
10	Min.	Positive		12		Unquestionable
11	Min.	Positive		2		Probable
12	MA	Positive	Tubercle bacilli	100	Pneumothorax	Probable
13	MA	Positive		0		Questionable
14	MA	Positive				Questionable
15	FA	Positive	Tubercle bacilli	8	Pneumothorax	Unquestionable

Review showed one case in which the diagnosis of tuberculosis could be questioned. The disease was limited to a thin-walled cavity that disappeared on bed rest. Examination for fungi had not been made.

Comparison of results in the early and late part of the study: The results of the bacteriological study are derived from a program that has become increasingly elaborate during the ten year period. The minimum schedule of examinations that will yield comparable results is not indicated. Table 5 shows the results for the first two years and the last two years of the study. There is very little difference in the percentage of positive findings (for cases of active pulmonary tuberculosis) in spite of the more extensive examination program carried out in the latter period. This is perhaps explainable by the fact that in the two years, 1936 to 1938, 8.2 per cent of the admissions (remaining two months or more) were mini-

mal cases and 34.4 per cent, far advanced; and in the two years, 1944 to 1946, 34.5 per cent of the admissions were minimal and only 14.7 per cent were far advanced cases.

DISCUSSION

The program for bacteriological diagnosis presented may be thought too elaborate for many institutions. It is not known how much it could be reduced without materially affecting the results. But as it stands it is well worth the cost in the resultant high caliber of clinical diagnosis and treatment.

There is much room for improvement in the program. Better culture media and culture methods are developing. More frequent gastric lavage is indicated.

But the success of any program depends on the development of as fool-proof a routine as possible, constant attention, vigilance and frequent reassessment of methods.

In the present classification all bacteriologically positive cases have been considered as having active disease regardless of other clinical findings. How does

TABLE 5

Comparison of Results in the Early and Late Part of the Study

Active cases of pulmonary tuberculosis resident two months or more

TWO-YEAR PERIODS	ADMITTED	BACTERIOLOGICALLY POSITIVE	
		Number	Per cent
1936 to 1938	99	96	96.9
1944 to 1946	123	120	97.6

this affect the results? If the clinically nonactive, bacteriologically positive cases were eliminated from the totals, the percentage of "negative" results would be somewhat raised.

It may be questioned whether it is possible to have any cases with clinically active disease that are completely bacteriologically negative. With an improved examination program, surely the proportion of "negative" cases will be reduced. In cases of strictly productive disease with well walled off tubercles or of well encapsulated caseous lesions, and in those in which the draining bronchus has been closed by collapse therapy or otherwise, no output of tubercle bacilli would be expected. The "closed" but "active" case is theoretically possible and does exist in practice.

It is believed that all cases rated bacteriologically positive are dependably so. A false positive result is considered to be far worse than failure to find tubercle bacilli that *are* present. As mentioned, the finding of rare bacilli on the microscopic preparations has not been accepted as a bacteriologically positive result. Concentration results have been checked by culture and questionable cultural growths by animal inoculation. The reading of microscopic, cultural, and animal tests has been closely supervised.

In comparing the results of different bacteriological programs it is important to know the clinical classification of the group studied. The percentage of positive bacteriological findings in a given series of patients will vary according to the proportion with advanced and minimal lesions. In the present series the proportion of minimal cases is unusually high, making up approximately one-quarter of the total, and that of the far advanced cases rather low, being only one-fifth of the total.

SUMMARY

1. An intensive program for the bacteriological diagnosis of tuberculosis is presented.

2. Where indicated, the program includes examination of two-thirds to four-fifths of all sputum expectorated by a patient during the first three months of residence by concentration and culture and, partly, by animal inoculation. In addition, stomach contents are examined by culture and inoculation once each month.

3. The evolution and use of this program during a ten year period is outlined.

4. During the ten year period positive bacteriological results were obtained in 97.4 per cent of clinically active cases of pulmonary tuberculosis resident two months or more.

5. Positive results were obtained in 94.6 per cent of cases of clinically active *minimal* tuberculosis resident two months or more.

SUMARIO

El Diagnóstico Bacteriológico de la Tuberculosis en un Sanatorio

1. El plan expuesto contempla el diagnóstico bacteriológico de la tuberculosis en forma intensa.

2. Siempre que esté indicado, el plan comprende exámenes de dos tercios a cuatro quintos de todo el esputo expectorado por un enfermo durante los primeros tres meses de su estancia en el sanatorio. Los exámenes comprenden concentración y cultivo del esputo y, en algunos casos, inoculación en animales. Además, se examina una vez al mes el contenido gástrico por medio de cultivos e inoculación.

3. Bosquéjanse la evolución y el empleo de este sistema durante un decenio.

4. Durante el decenio del estudio obtuviéronse resultados bacteriológicos positivos en 97.4 por ciento de los casos clínicamente activos de tuberculosis pulmonar en residencia dos meses o más.

5. Obtúvose igualmente resultado positivo en 94.6 por ciento de los casos de tuberculosis *minima* clínicamente activa que habían residido en el establecimiento dos meses o más.

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LETTER TO THE EDITORS

USE OF A SLIDE CULTURE TECHNIQUE FOR RAPID STREPTOMYCIN SENSITIVITY TESTING

To the Editors of the American Review of Tuberculosis:

We have found it possible to perform streptomycin sensitivity tests employing a modification of the slide-culture method first described by Pryce. (Pryce, D. M., J. Path. Bact., 1941, *53*, 327.)

For the past year we have been comparing this method with standard techniques of performing sensitivity tests with most promising results.

The method is rapid, easily performed, and is carried out as follows:

Pure cultures, or digested neutralized specimens, are smeared thinly over the surfaces of 5 sterile 3 by ¾ inch glass slides (made by cutting a 3 by 1 microslide longitudinally). Employing sterile slide forceps, the smear preparations are immersed into a series of tubes of Tween-albumin medium. (Dubos, R. J., Proc. Soc. Exper. Biol. & Med., 1945, *58*, 361) containing 0, 0, 2, 10, and 100 γ of streptomycin.) Other suitable liquid media may be employed.

After incubation at 37°C. for one week, a smear is removed from a control tube (no streptomycin) and is stained by the usual Ziehl-Neelsen technique. The preparation is examined by low power microscopy and, if colonies with serpentine cords (Middlebrook, G., Dubos, R. J., and Pierce, C., J. Exper. Med., 1947, *86*, 175) are seen, the remainder of the smears are also removed, stained, and examined in a similar manner. The concentration of streptomycin which inhibits growth on the slide is considered the end point.

The sensitivity readings compare favorably with tests made, using more standard methods employing inspissated egg media and egg-yolk-agar medium. It was interesting to note that one could estimate "partially resistant" strains by comparing colony size and numbers of colonies with the growth on the control tube.

We have also attempted to utilize this technique by smearing selected particles from pathological material directly on the slide and decontaminating the preparation by immersing it in 5 per cent H_2SO_4 or 3 per cent NaOH. Although positive results have been obtained, they have been too erratic to recommend this procedure unless duplicate series of smears are made.

It is our hope that other laboratories will evaluate this technique as a rapid method for testing the sensitivity of *M. tuberculosis* to streptomycin or other antibacterial agents.

U. S. Public Health Service
Tuberculosis Evaluation Laboratory
Atlanta, Georgia.
March 15, 1949

Martin Cummings,
Margaret Drummond

THE

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ABSTRACTS

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Childhood Tuberculosis.—Most reports of tuberculosis in children confine themselves to a study of the primary complex. The disease may travel diverse paths, however, and the character may be protean. A study of 90 cases which came to autopsy at Sea View Hospital is reported. All the patients were less than 13 years of age, and 40 per cent less than 3. There were 67.8 per cent Negro children in the series, a reversal of the over-all ratio in the hospital. The reason would seem to be the presence of a low resistance and consequent overwhelming infection in this group, with frequent progressive primary complexes and dissemination. There were 3 general types of disease: the primary complex, hematogenous dissemination, and chronic pulmonary tuberculosis. The frequency of various lesions was as follows: (*1*) Healed or healing primary complex occurred in 66 cases. (*2*) Progressive primary complex was seen in 23 cases. The lymph nodes were often grossly involved, both locally and in distant sites. (*3*) Early generalized hematogenous tuberculosis was present to some extent in all 23 cases of progressive primary complex. (*4*) Late generalized hematogenous lesions occurred in 6 cases, all of which had active extrapulmonary disease. (*5*) Chronic pulmonary tuberculosis was present in 20 cases. This incidence in children (22 per cent of the series) is notably higher than in other reports. The lesions were similar clinically and roentgenologically to lesions in older age groups. A difference at autopsy was the frequency (7 cases) of caseated regional nodes in children, a rare finding in chronic pulmonary lesions of adults. (*6*) Skeletal tuberculosis was present as an active disease in 21 cases. All of the 13 cases with vertebral lesions had associated abscesses. All but one of the cases of bone disease came from progressive primary lesions. (*7*) Genito-urinary lesions were present in 10 cases, 9 of which were females. Three of the cases had renal lesions; 8 had genital lesions, chiefly of the fallopian tubes. (*8*) Thirty-seven cases of fatal tuberculous meningitis were included, a far greater incidence than in adults. Tuberculomas of the brain were present in 78 per cent of these. The sources of the brain lesions were fresh primaries in 5 cases, progressive primaries in 12, healed primaries in 17, and active extrapulmonary disease in only 3. (*9*) Two cases of extensive intestinal ulceration without pulmonary cavitation were found. (*10*) One case of tuberculous valvular endocarditis was noted. This is so rare that it may be the eighth case described in the literature.—*Tuberculosis in children, O. Auerbach, Am. J. Dis. Child., April, 1948, 75: 555.*—(*W. H. Oatway, Jr.*)

Phthisiogenous Infiltrates.—Laennec, Koch and their contemporaries believed that pulmonary tuberculosis started in the apices and spread apicocaudally. This conception was maintained into the Nineteen-twenties. In 1922 Assman demonstrated a form of isolated tuberculosis in adults which Simon named *"Frühinfiltrat"*. Braenning and Redeker developed the thesis that this is a clinical-roentgenological entity and concluded that most tuberculosis originated from these infraclavicular "early infiltrates" which spread

not apicocaudally but in periodical propagations. During the past twenty years this doctrine of "early infiltrates" has been shown to be essentially wrong. Scandinavian researches notably by Heimbeck, Scheel, Malmros and Hedvall and Frostad showed that some of these "early infiltrates" were primary infiltrates. They also found that pulmonary tuberculosis originated from "subprimary" initial foci situated in the supraclavicular region or first intercostal space or in both regions twelve to fourteen months after the primary infection. The variation is one of time, acute as contrasted with subchronic or chronic development after a primary infection. Following BCG vaccination, a typical "early infiltrate" may appear in the lung. Pulmonary tuberculosis may develop from hematogenous foci after secondary spread, from isolated hematogenous infiltrates, and finally from exogenous or endogenous reactivated infiltrate-residues. Thus destructive phthisis may develop from infiltrates or residues of infiltrates which differ as to genesis, aspect and age. These are all phthisiogenous forms of infiltrates.—*On the different forms of phthisiogenous infiltrates and the development of phthisis, N. Christiansen, Acta radiol., 1948, 30: 17.—(J. E. Farber)*

Renal Tuberculosis.—A tuberculous stricture of the ureter is most likely to occur at (*1*) the uretero-pelvic junction, (*2*) the juxtavesical portion or (*3*) the point where it crosses the pelvic brim. The formation of a stricture may lead to abatement of vesical symptoms as the result of one of the following changes: (*1*) tuberculous hydronephrosis, (*2*) extensive renal caseation with or without infiltration of calcium salts, or (*3*) fibrosis, the so-called "autonephrectomy". The first two types are sources of danger by rupture, secondary infection, or miliary tuberculosis. The three types are seen in 20 per cent of all cases of renal tuberculosis; type 3 alone is seen in 0.5 per cent. Calcification is not *per se* a favorable sign. With an obstructed ureter, kidney disease may not be suspected so that other abdominal conditions may be considered first or evidence of the condition may be noted in a routine investigation of a case of tuberculosis. In the roentgenogram, the kidney outline is enlarged, with or without intrarenal or ureteral calcification. The intravenous pyelogram shows nonfunction of the kidney. On cystoscopic examination, the ureteric orifice is puckered and scarred; it may be difficult to pass a catheter. The treatment is surgical removal of the kidney and ureter. If the condition appears quiescent, operation may be deferred; clinical criteria are more important than roentgenographic findings in this decision.—*Silent renal tuberculosis, J. H. Carver, Tubercle, December, 1948, 29: 269.—(A. G. Cohen)*

Extrafascial Pneumothorax.—In certain cases, after a first stage thoracoplasty with Semb apicolysis, complications arise which delay or prevent the performance of additional stages. In such cases it is desirable to retain the benefits of the first stage. In other cases, with small apical cavities, a three-rib thoracoplasty suffices. In both situations, the author used air to keep open the Semb space. Insufflations were begun during the second postoperative week. Refills were continued for six months, by which time the regenerated ribs could keep the apex down. In some cases, oil was substituted for air. In a series of 31 cases, 7 were unsuccessful due to various complications. In the others, the original collapse was maintained until and after the space was allowed to obliterate. Thus additional stages were delayed safely. In 9 patients with small apical cavities, additional stages were not required.—*Extrafascial pneumothorax, M. Konstam, Thorax, December, 1948, 3: 247.—(A. G. Cohen)*

Hemorrhage in Extrapleural Pneumothorax.—Calcium alginate was found experimentally to possess hemostatic properties. In the operation for extrapleural pneumothorax, the walls of the space were painted with a 4 per cent solution of sodium alginate; this was followed by application of 2 per cent calcium chloride. The procedure appeared to control

hemorrhage effectively without untoward effects.—*The control of haemorrhage in extrapleural pneumothorax, K. S. Mullard, Thorax, December, 1948, 3: 233.—(A. G. Cohen)*

Artificial Pneumoperitoneum.—Peritoneal effusion is the most common of the infrequent complications of artificial pneumoperitoneum used in the treatment of pulmonary tuberculosis. It has occurred in 8 (3.58 per cent) of 223 cases who had received 5,800 refills. The ascites in these cases is often due to tuberculous peritonitis. Its incidence is unrelated to the activity of the pulmonary disease. Adhesions appear early but the response to laparotomy is fairly good. The appearance of ascites is considered an indication for discontinuation of the pneumoperitoneum.—*Peritoneal effusion as a complication of artificial pneumoperitoneum, R. C. Cohen, Lancet, December 25, 1948, 2: 1006.—(A. G. Cohen)*

BCG Vaccination.—Ninety per cent of infants from homes with infectious tuberculosis in Dublin become infected during the first year of life. Autopsy evidence shows that most deaths resulted from direct spread from the unhealed primary complex. In more recent years, as the result of better and more prompt treatment, there were more recoveries; still, in the best year at least 41 per cent died. Sixty infants under the age of one year were vaccinated with BCG and then returned to tuberculous homes. They were followed for one to ten years. There were no deaths from tuberculosis.—*The need for BCG vaccination in infants, D. S. Price, Tubercle, January, 1949, 20: 11.—(A. G. Cohen)*

BCG Vaccination.—There is a very high incidence of tuberculosis among the Saskatchewan Indians. For a period of about thirteen years, alternate infants were given BCG vaccination. A total of 306 infants were vaccinated and 303 were followed as controls. The alternation was arranged in such a fashion as to insure comparability of the vaccinated and control groups. Vaccinations were performed within ten days of birth. In all but 21 cases, the intracutaneous route was used. Approximately one-half of the infants in each group were in close contact with infectious adult tuberculous patients. Follow-up data were available for almost all cases. In the vaccinated group, there were 6 cases of tuberculosis (1.96 per cent) with 2 deaths. In the control group, there were 29 cases of the disease (9.5 per cent) with 9 deaths. The ratio of incidence of infection in the 2 groups was 1:4.85; the ratio of deaths was 1:4.5. There were no untoward effects from the vaccination. —*BCG vaccination of Indian infants in Saskatchewan, R. G. Ferguson & A. B. Simes, Tubercle, January, 1949, 30: 5.—(A. G. Cohen)*

BCG Vaccination.—In autopsies performed upon children who died of contagious diseases, special studies were made of the various chains of lymph nodes and also of the tonsils, liver, kidneys, spleen and lungs. The subjects included 57 children under the age of two years who had been vaccinated with BCG-Paris and 25 controls. Characteristic changes were found up to three months after vaccination. The lymph nodes contained large dilated sinuses filled with large endothelial cells and lymphoblasts. Reticulum cells were scarce; monocytes and histocytes were absent. The afferent lymphatics were filled with a pale, rose-colored homogeneous substance. The lungs showed accumulations of histiocytes and lymphocytes. The interalveolar and interlobar septa and pleura were thickened and edematous and the alveoli were distended. The spleen contained hyperplastic follicles and endothelial proliferation. Round cell infiltrations of the liver were noted. In the group vaccinated three to six months previously, the changes were less marked. After one year, there was progressive fibrosis of the lymphatic apparatus. After two years, the nodes contained increasing young connective tissue elements while fibrous tissue was more pronounced at

the periphery. Fibrous strands projected radially into the gland substance. The lungs, liver and spleen showed few changes. It was concluded that the cellular reaction to BCG starts in two to three weeks, reaches its height in the third month and then declines. At the end of one year there is beginning progressive fibrosis.—*Pathologic changes in children vaccinated with BCG, V. I. Puzik, Amer. Rev. Soviet Med., October, 1948, 5: 189.*—(*A. G. Cohen*)

Vitamin A for Skin Tuberculosis.—In 45 patients with skin tuberculosis a low vitamin A level in the blood was found in association with a high carotene content. Administration of 50,000 units of vitamin A daily for three to four months produced normal values in the blood. Epithelization of ulcerations and absorption of lupus infiltrates was observed in 27 patients treated with this dosage. Improvement was noted in 21 of the 27 patients, 16 showing marked improvement and 5 moderate improvement. No clinical cure was achieved in lupus whereas 4 of 6 cases of scrofuloderma appeared clinically healed. The therapeutic results of vitamin A were enhanced if combined with vitamin C administration.—*Vitamin A and its importance in skin tuberculosis (Russian), V. L. Althausen and M. V. Lepskaia, Probl. Tuberk., 1948, 1: 57.*—(*V. Leites*)

Calciferol for Lupus.—Fifty cases of lupus were treated with calciferol. In 38 of these cases the disease had lasted from five to fifteen years, in 12 from twenty to thirty-five years. The daily dosage was 100,000 to 200,000 international units in an alcoholic solution and was given for four to six months. Of the 50 patients, 33 appeared clinically cured, 6 were markedly improved, and 11 moderately improved. The patients in the latter two groups were still being treated. The stability of the results and the incidence of relapse must be evaluated later but biopsy specimens of the skin and mucosa in cases appearing clinically cured showed anatomical healing in 3 of the 11 cases examined. All other speciemens revealed persistence of tubercles and giant cells. Complicating gastro-intestinal and urinary disturbances were found in 40 per cent of the cases but they were of a mild and transitory nature.—*Treatment of lupus with vitamin D_2 (Calciferol) (Russian), A. B. Weinstein, V. L. Althausen, & A. R. Tatianin, Probl. Tuberk., 1948, 5: 31.*—(*V. Leites*)

Vitamin D in Sarcoidosis.—Because favorable results have been obtained with vitamin D in the treatment of lupus vulgaris, the lesions of which resemble sarcoidosis, vitamin D therapy was tried in the latter. A case is reported of a woman who was known to have had sarcoidosis of the skin of the face for nine years with no remissions and whose chest roentgenograms showed prominent hilar shadows. She did not react to the first Mantoux test; on retesting there was a reaction at 72 hours although there was none at 48 hours. She was given 100,000 units of calciferol daily by mouth for fifteen days, when toxic symptoms developed and the treatment was stopped. There was no rise in the serum calcium at this time but the blood urea nitrogen rose to 60 mg. per 100 ml. There was dramatic improvement of the skin lesions. She later had another course of calciferol 50,000 units every second day, and again became intolerant. The clinical improvement remained and it is believed that the drug favorably influenced the sarcoidosis of the face. There was slight progression of the cystic changes of the fingers, however, and the roentgenographic appearance of the chest was not altered; her bronchitic symptoms became worse. Calciferol should not be used in the treatment of sarcoidosis unless the skin lesions are of sufficient severity to justify the risk of these untoward reactions.—*Vitamin D in treatment of Boeck's sarcoidosis, R. F. Robertson, Brit. M. J. December 18, 1948, 4589: 1059.*—(*R. W. Clarke*)

Roentgenotherapy of Sarcoidosis.—Sarcoidosis runs a chronic, relapsing course often with mild symptoms but sometimes

with great damage to many structures. Many forms of treatment, including roentgenotherapy, have been unsuccessful. The authors report 11 cases in which they employed roentgenotherapy to various areas, including the skin, eyes, lymph nodes, and lungs. In one patient, skin nodules disappeared after doses of 3,000 and 2,500 r. but another nodule in the same person did not regress with 2,000 r. The lesions of one patient regressed spontaneously eleven months after irradiation was completed.—*X-ray therapy of Boeck's sarcoid, C. P. Donlan, Radiology, August, 1948, 51: 257.*—(*G. F. Mitchell*)

Heterospecific Therapy for Tuberculosis.—Experiments begun in 1924 demonstrated the production of a "heterospecific increase of resistance" when animals were inoculated with vaccines prepared from a variety of common bacteria. Rabbits and guinea pigs were more resistant than usual to pathogenic bacteria, including *Mycobacterium tuberculosis* for five to twenty days after intravenous or subcutaneous inoculation with dead bacteria. The greatest protection was obtained by using a mixture of heat-killed *E. typhosa* and *N. gonorrhoeae* in a ratio of 1:3. *E. typhosa* is said to stimulate the function of the reticulo-endothelial system and *N. gonorrhoeae* to produce an infiltration of plasma cells. Weekly subcutaneous inoculations with this mixture partially protected the animals against subsequent injections of tubercle bacilli and favorably altered the course of an established tuberculous infection. A total of 283 tuberculous patients were treated with the vaccine prior to 1937 and the results were considered "favorable." In 1940 a mixed autolysate of *E. typhosa* and *N. gonorrhoeae* ("Heterosate") was found to be more effective than the vaccines in the prevention and treatment of experimental tuberculosis in animals. From 1940 to 1945, 932 tuberculous patients were treated with "Heterosate." In preparing this material a clear autolysate was obtained from a suspension of 2.0 mg. of bacteria per cc. The autolysates from *E. typhosa* and *N. gonorrhoeae* were then mixed in a 1:3 ratio. Weekly subcutaneous inoculations were begun with 0.25 cc. of a 1:100,000 dilution and the inoculum was increased over a period of thirty weeks to 1.0 cc. of undiluted "Heterosate." The course of treatment consisted of 36 to 176 inoculations. Of 300 patients with "incipient" tuberculosis, 65 improved and 235 completely recovered; of 403 "light cases", 86 improved and 315 recovered. The course of the disease was not changed in 2 "light cases" with pleurisy. "Moderately severe" disease was improved in 88 and cured in 65 of 173 patients; 18 were unchanged and 2 died. Of 56 "serious cases", 19 improved, 7 recovered, 25 were unchanged, and 5 grew worse. Prophylactic inoculations of "Heterosate" apparently afforded some protection against tuberculosis in a series of 44 student nurses.—*Heterospecific alteration therapy for pulmonary tuberculosis, S. Nukada & C. Ryu, Japanese Med. J., June, 1948, 1: 181.*—(*L. B. Hobson*)

Congenital Pneumonia.—An epidemiologic and serologic relationship exists between the occurrence of simple upper respiratory infection and primary atypical pneumonia. Primary virus pneumonitis occurs in epidemics attacking newborn and premature infants. Surface cells from the pharynx and lungs often contain cytoplasmic inclusion bodies but bacteria are scanty. Treatment is ineffective. Six instances are reported in which infants were born with respiratory symptoms or developed them during the first or second day. The mothers had symptoms of respiratory infection before or after childbirth. Both infants and mothers were found to have inclusion bodies in the pharyngeal smears. Normal human serum, U.S.P., and concentrated human gamma globulin appeared to be beneficial for the infants' infections.—*Congenital pneumonitis in newborn infants, J. M. Adams, Am. J. Dis. Child., April, 1948, 75: 544.*—(*W. H. Oatway, Jr.*)

Lungs in Scleroderma.—In 4 cases of

generalized scleroderma, chest roentgenograms showed diffuse, irregular, fibrotic lesions throughout both lower lung fields. In these, as well as in most previously reported cases, there were no pulmonary symptoms aside from progressive exertional dyspnea. The changes are probably due to increase in pulmonary connective tissue. The pulmonary condition may precede the appearance of skin changes. It may be found also in patients with the Raynaud phenomenon but without scleroderma.—*Pulmonary fibrosis in generalized scleroderma, W. E. Lloyd & R. D. Tonkin, Thorax, December, 1948, 3: 241.*—(*A. G. Cohen*)

Atypical Pneumonia.—Between March, 1945 and March, 1946, the authors saw 49 cases of lobar pneumonia of which less than 10 per cent showed the typical picture. In the other cases the disease began gradually with a slow rise of temperature and subfebrile temperatures were observed through many weeks. Repeated episodes of slight fever, however, were common. Bronchial breathing was hardly ever heard but crepitant rales were present for a long time. Herpes labialis was rare. The leucocyte count was rarely more than 10,000. In 26.4 per cent of the patients, roentgenologic examinations showed pulmonary infiltrations present after four weeks. There was no difference in the course of the disease in 25 patients treated with sulfonamids as compared to that in 24 patients who received the old treatment with quinine and camphor. There was a mortality of 32 per cent. It is believed that the atypical course in these patients was due to their poor nutrition, especially the lack of protein and vitamins in their food.—*Uber die besonders Verlaufsform der Pneumonien des letzten Jahres, W. Groeger & E. Treml, Wien. klin. Wchnschr., December 5, 1947, 59: 794.*—(*G. C. Leiner*)

Pulmonary Hemosiderosis.—The rare disease of pulmonary hemosiderosis was first described in 1921. The patients have cyanosis and dyspnea in early life with a cough productive of a blood-tinged sputum containing hemosiderin. Anemia, eosinophilia and leukopenia may appear. Fever and an elevated sedimentation rate also occur. Physical examination reveals dulness over the lung, harsh breath sounds, and rales. The roentgenographic picture is pathognomonic, with diffuse shadows scattered more or less over both lung fields, absolutely independent of the boarders of the lobes and sometimes denser toward the bases. This cloudiness, however, often alternates with a mossy mottling. In the early stages mottling is a dominating feature. The hilar shadows are enlarged and deepened. The alveoli are more or less filled with iron pigment, thus reducing the air content. Treatment is symptomatic and death is the final outcome in spite of remissions.—*Hemosiderosis of the lungs—Typical roentgenological findings, O. Elgemark & S. R. Kjellberg, Acta radiol., 1948, 29: 32.*—(*J. E. Farber*)

Pulmonary Manifestations of Leukemia.—A case of myelogenous leukemia in a 3 year old girl is reported. The respiratory symptoms were predominant in the clinical picture and consisted of dyspnea, cough, bloody expectoration and fever. Roentgenograms showed diffuse mottling in both lung fields. The tuberculin test was negative. At autopsy the lungs were generally congested with numerous infarcts and intra-alveolar edema. The interalveolar septa were extensively infiltrated with leucoblastic and monocytic elements.—*Leucémie aiguë à forme pulmonaire chez une fillette de 3 ans, R. Clément et R. Gormezano, Presse méd., June 13, 1948: 446.*—(*V. Leites*)

Retrosternal Infiltration in Malignant Lymphoma.—There are no dependable pathognomic roentgenographic signs of intrathoracic lymphomas and they may assume many different forms. The authors find that, in addition to the six types generally described, there is also a retrosternal type occurring alone or with one of the other forms. This finding may be correlated with the anatomic distri-

bution of lymphoid tissue in the retrosternal area. Enlargment of the hilar or mediastinal lymph nodes usually is looked for when a clinical diagnosis of malignant lymphoma is made, but the other manifestations may be neglected. The authors have found a lateral roentgenogram of the chest helpful in demonstrating (*1*) a "boardlike" soft tissue mass of even width extending from level of diaphragm to that of the sternoclavicular joint, or (*2*) a "padlike" mass or masses with a lobulated appearance and a broad base toward the sternum.—*Retrosternal infiltration in malignant lymphoma, F. G. Fleischner, C. Bernstein & B. E. Le Vine, Radiology, September, 1948, 51: 350.*—(*G. F. Mitchell*)

Peripheral Vascular Diseases of the Lung.—Various disease states affect the smaller pulmonary blood vessels by increasing the permeability of their walls or by causing obstruction of their lumina. The authors are concerned with the roentgenographic changes which are seen in diseases affecting vascular permeability. This permeability may be disturbed by (*1*) trauma which may alter the vessel wall, rupture it, or produce prolonged arteriolar spasm, (*2*) chronic nutritional deficiency, or (*3*) exposure to drugs or antigenic substances. Nonpenetrating injuries of the chest frequently produce roentgenographic signs suggestive of an acute inflammatory process. These include parenchymal shadows of variable extent usually associated with pleural involvement and tending to disappear rapidly. Epidemic influenza damages the pulmonary capillaries primarily, producing a progressive hemorrhagic pneumonia with shadows rapidiy extending from the periphery toward the hilum. Disseminated lupus erythematosus shows a roentgenographic picture similar to that in influenza but is, of course, characterized by diffuse fibrinoid degeneration of collagen with necrotizing arteritis. Rheumatic fever also is associated with widespread collagenous degeneration and vascular changes. There may be many areas of perivascular exudation which form nodules during healing. The lungs are involved in about half the patients during the acute stages and later roentgenograms show a diffuse, hazy shadow over the middle and upper portions of the lung fields, more dense peripherally. If heart failure and pulmonary congestion are present, these findings are obscured. Periarteritis nodosa is a focal arteritis with hyaline degeneration, nodule formation, and obliteration of the lumen. Most patients with this disease have pulmonary involvement at some time and may have pulmonary failure in the acute stages. This is associated with transient but massive, symmetrical shadows extending from the hilum toward the periphery so that a "corona" appears about the mediastinum. In the chronic stages small, hazy shadows scattered throughout the peripheral lung fields and accentuated bronchovascular markings at the bases suggest bronchopneumonia. Serial films show migrations of these shadows similar to those described in Loeffler's syndrome. Exfoliative dermatitis may be accompanied by roentgenographic evidence of a diffuse inflammatory process, disappearing and reappearing with the changes in the skin. Acute glomerulonephritis may alter the permeability of the vascular walls and produce evidence of pulmonary edema and pleural effusion.—*The roentgen appearance of the chest in diseases affecting the peripheral vascular system of the lungs, R. P. Barden & D. Cooper, Radiology, July, 1948, 51: 44.*—(*G. F. Mitchell*)

Surgery of Tension Cysts.—Congenital cysts of the lung are uncommon. A survey in 1933 included only 150 cases, very few of which were seen in infants or diagnosed during life. The large single tension type of cyst is even more rare. It is bronchogenic in origin and until recently was fatal. In the past five years a few resections have been reported and the authors successfully removed a giant cyst in an infant of four months. The patient's mother had had four previous pregnancies, two of which had resulted in miscarriages and one in a stillbirth; the other infant died during the first day of life. The

patient breathed rapidly from birth but became acutely dyspneic only two days before hospitalization. A roentgenogram of the chest showed an air-filled sac occupying most of the right hemithorax, bulging to the left of the midline, and markedly displacing mediastinal structures to the left. Preliminary decompression by needle and catheter, as suggested by Gross, was done. This procedure gives rise to complications but it allows a return towards normal anatomy and physiology, and aids in controlling infection. After decompression, most of the cyst wall, which was in the middle lobe, was removed at operation. The right upper and lower lobes were expanded at the conclusion of surgery, and the postoperative course and result were good.—*Tension type of congenital pulmonary cyst, J. M. Walker, W. B. Taggart & H. J. Staton, J. Pediat., November, 1948, 33: 601.*—(*W. H. Oatway Jr.*)

Surgery for Tracheal Compression.—A new method is described for the relief of compression of the trachea by an anomalous artery. An infant had signs and symptoms of tracheal stenosis from birth. For four months the breathing was noisy and wheezing, dyspnea without cyanosis was present, but oxygen was often needed. Rhonchi were heard throughout the chest; leukocytosis and fever were often present. The child insisted on lying in a posture of opisthotonos with the head held in hyperextension. Iodized oil in the trachea showed a defect just above the level of the aortic arch. At operation the right innominate artery was found to arise slightly to the left of the normal position in a common origin with the left common carotid and to press on the right anterolateral surface of the trachea. Rather than interrupt the artery, the surgeon dissected it free from the trachea and sutured it to the periosteum of the posterior surface of the mannbrium sterni. The convalescence was satisfactory, the symptoms and signs clearing at once, and a tracheogram showed only a slight residual defect.—*Compression of the trachea by an anomalous innominate artery: An operation for its relief, R. E. Gross & E. B. C. Neuhouser, Am. J. Dis. Child., April, 1948, 75: 570.*—(*W. H. Oatway, Jr.*)

Multiple Port Irradiation of Deep-seated Tumors.—Roentgenotherapy of deep-seated, malignant tumors, especially of the esophagus and lungs, has been unsuccessful, in part because of the difficulty of delivering a large enough dose to the tumor without damaging the overlying tissues. In recent years, this difficulty has been avoided by several methods including one in which the patient is rotated with the tumor as the axis of rotation during irradiation. The authors have modified this rotation therapy by irradiating multiple fixed fields with the beam so directed that it always passes through the tumor. By this means intensive irradiation is delivered to the tumor while each skin area receives only a fraction of the total dose. The exact extent and site of the tumor must be known, of course, in planning the treatment. Twelve narrow portals of entry on the back and chest and in the axillae are used for tumors of the esophagus or hilar region. Fewer portals are used for pulmonary neoplasms which are more eccentrically located. Carcinoma of the esophagus is especially suited to this form of treatment but solitary tumors of the hilar region and of the lung parenchyma also respond. Gratifying results have been obtained with relief of symptoms, prolongation of life, and reduction in the size of the tumor.—*Treatment of deep-seated malignant tumors with multiple port technic simulating rotation therapy, I. I. Kaplan & S. I. Etkin, Radiology, August, 1948, 51: 188.*—(*G. F. Mitchell*)

Promizole for Military Tuberculosis.—In general, tuberculosis in adults does not respond well to promizole. However, it was decided to employ this drug at Bellevue Hospital in New York for the treatment of certain forms of tuberculosis in children. It was first used in 5 successive cases of meningitis with no observable beneficial effects.

Acute generalized hematogenous tuberculosis was then selected for treatment with promizole because the course of this disease is more prolonged than that of meningitis, thus allowing more time for the action of the drug. The prognosis of this form of tuberculosis in children is nevertheless uniformly bad. The first cases were started on 1 Gm. daily and the dose was increased rapidly to the point of toxicity. Later the dosage was more slowly increased until a daily dosage of 5 Gm. was reached. A blood level of 2 to 3 mg. per 100 cc. was found satisfactory and, after prolonged treatment, adequate blood levels could be obtained with as little as 1 Gm. a day of the drug. Eleven children, ranging in age from six months to eleven years, with acute miliary tuberculosis received promizole. Treatment was given for one month to two or more years. The toxic effects noted were vomiting, leucopenia, cyanosis, jaundice, a definite increase in the size of the thyroid gland and sex maturation as evidenced by enlargement of the nipples and breast tissue and growth of pubic hair. These changes yielded readily to treatment except possibly the sex maturation. Five consecutive cases of acute generalized miliary tuberculosis were apparently adequately treated with promizole. Of these 2 children died forty-three days and four and a half months after therapy was begun. Roentgenographic evidence of miliary tuberculosis disappeared completely in 3 children who are alive thirty to thirty-three months after promizole was first given. The primary pulmonary lesions cleared slowly and in 2 cases cavitation appeared. One child developed tuberculosis of the spine, choroiditis and positive urine cultures while taking the drug. All three of these cases are still receiving maintenance doses of promizole. Thus promizole may have a favorable action in suitable cases of miliary tuberculosis. It can be given safely and effectively over a period of years.—*The treatment of miliary tuberculosis with promizole. E. M. Lincoln, S. Stone & O. R. Hoffman, Bull. Johns Hopkins Hosp., January, 1948, 82: 1.* (*J. S. Woolley*)

Streptomycin for Tuberculous Meningitis. Thirty children with tuberculous meningitis between the ages of 9 months and 11 years were treated with streptomycin. The drug was administered intramuscularly as well as intrathecally to 25 patients; 5 others were treated with intrathecal injections alone. A series of 20 to 25 intrathecal injections was given, each dose being 0.025 to 0.1 Gm. The intramuscular dosage was 0.25 to 0.5 Gm. daily and was continued for three to five months. Among these 30 cases there were 11 deaths; 19 children were alive after two to fifteen months. The best results were obtained in those children in whom treatment was started not later than on the tenth day of illness. The spinal fluid became completely normal in only 6 of the surviving 19 cases.—*Streptomycin in tuberculous meningitis in children* (*Russian*), *N. O. Vassilevich, Probl. Tuberk., 1948, 5: 22.*—*V. Leites*)

Streptomycin in Chest Surgery.—Reports of the use of streptomycin in pulmonary and pleuropulmonary infections are still scanty. A series of 17 cases of lung abscess, nontuberculous empyema, and tuberculous empyema is reported as a part of the experience with streptomycin in U. S. Army Hospitals. In 3 cases of lung abscess the drug in conjunction with penicillin seemed helpful when the organisms were sensitive but not when the lesions were chronic and extensive. Five cases of nontuberculous empyema were helped remarkably, especially when susceptible organisms, notably *E. coli*, were present and adequate surgical drainage was obtained. In 9 cases of tuberculous empyema the results were variable. Fistulas and empyemas did not seem to improve if the associated pulmonary lesions were productive or if they did not improve coincidentally. It is believed that streptomycin may be more effective in conjunction with penicillin; it may control pyogenic invaders during local or intramuscular administration; and it may extend the scope of plastic operations by providing additional protection.—*Streptomycin in surgical*

infections: VI. Lung abscess and empyema, E. J. Pulaski & T. T. White, Ann. Surg., August, 1948, 128: 312.—(*W. H. Oatway, Jr.*)

Treatment of Pneumococcal Pneumonia.—The authors set out to determine whether it was necessary to maintain appreciable blood concentrations of penicillin in the treatment of pneumococcal pneumonia. Experimental evidence had indicated that it was not necessary. Seventy-nine patients were given 300,000 units of aqueous crystalline penicillin G every twelve hours. In previous years 69 patients had received aqueous penicillin every three hours, while 58 had received penicillin in oil and beeswax. The results of the newer method were just as good as the others.—*Pneumococcal pneumonia treated with aqueous penicillin at twelve hour intervals, P. A. Tumulty & G. Zubrod, New Engand J. Med., December 30, 1948, 239: 1033.*—(*A. G. Cohen*)

Penicillin for Lung Abscess.—Sixty cases of lung abscess were treated with endobronchial instillations of penicillin immediately after discovery. Healing of the abscess was considered to have been achieved under the following conditions: (*1*) disappearance of symptoms and of roentgenographic abnormalities with normal bronchograms for a period of at least six months; or (*2*) disappearance of the abscess cavity on the roentgenogram with some remaining density or slight sequelae on bronchography such as the demonstration of small isolated bronchial dilatations, dislocated bronchi, or a small single cavity two years after the cessation of symptoms. Each patient received an average of 8 instillations through a bronchial catheter. Of the 60 patients treated with this method, 30 had a follow-up period sufficiently long to be evaluated by the above criteria of cure. Fifty per cent of these patients had no residual roentgenographic abnormalities. Twenty-five per cent were considered healed but had residual changes, often demonstrable only by bronchography. There were 15 per cent failures with multiple recurrences. Ten per cent died of other causes or could not be followed. The patients who do not respond to this treatment must be considered candidates for excisional surgery which should not be delayed too long.—*Quelques problemes posés par la penicilline endo-bronchique dans le traitement des abcès du poumon, H. Métras, M. Grégoire, I. Lieutier, C. Gaillard, Presse méd., July 3, 1948: 471.*—(*V. Leites*)

Routine Roentgenography.—The results of annual roentgenography of the employees of large banking and commercial enterprises in Paris are reported. In a group of 6,000 employees between the ages of 16 and 60, annual roentgenographic surveys were done from 1942 until 1948. The authors compare the results of the case finding program of regular annual surveys with case finding due to other activities of the medical department of the enterprise ("occasional case finding"). The latter activities were: (*1*) preemployment examinations, (*2*) chest examination at the time of intercurrent illness or in the presence of suspicious subjective symptoms, (*3*) chest examination occasioned by the conversion of the tuberculin reaction. Tuberculin testing was routinely carried out on all employees below the age of 25 and repeated every three months as long as there was a negative reaction. In 1942 when "occasional case finding" was not yet well organized, annual roentgenography detected 4 cases of active pulmonary tuberculosis among 2,880 employees (0.14 per cent). In 1943 one case was found among 3,022 persons. In 1945 and 1946 no cases were discovered. In 1947 there was one case among 4,500 and in 1948 one case among 5,938 persons. Thus, from 1943 until 1948 only 3 cases of active tuberculosis were discovered by annual roentgenographic surveys. During this same period more than 30 cases of active pulmonary tuberculosis were found in this employee group by means other than the annual examination, 24 by the medical department itself and 6 by the family physician or the district tuberculosis clinic. Another survey conducted in 1948 discovered among 5,840 bank employees only one case (10.02 per cent) of active pulmonary tubercu-

losis which was unknown to the medical department. In view of these meagre results the value of annual roentgenographic surveys is considered absolutely out of proportion to the cost in stable and homogeneous employee groups supplied with a good medical department. Much more important is the continuous case finding activity of the medical department especially on the occasion of the slightest suspicious symptoms.—*La tuberculose et les examens radiologiques annuals, G. Poix, M. Barièty, & J. Benetaud, Presse med., November 16, 1948: 776.*—(*V. Leites*)

Case Finding in Hospitals.—The routine examination by roentgenography of hospital admissions and outpatients is one of the best methods of finding tuberculous and other lesions of the chest. Although early trials occurred fifteen years ago, no hospital was known to have a routine program in 1938. A survey in 1943 indicated that 56 general hospitals were using the method but recent data on progress have been either incomplete or unusable. The American Hospital Association reported early in 1948 that 879 institutions of all types claimed to be taking "routine chest x-rays." An attempt has been made to determine the practice in general hospitals which comprise 4,539 of the 6,276 registered hospitals but which receive 93 per cent of the 15,829,000 admissions per year. Information was obtained from all of the state health departments, 43 of which now have tuberculosis control officers. It was found that data on the origin of funds and on the type of films were scanty. Data on the cost per patient and the charges per film were usually not computed or correlated. In most hospitals the taking of chest roentgenograms is far from routine. In spite of a lack of definite statistics, there is evidence that the use of routine roentgenography is being widely extended. Several states have very active and widespread plans. Finances are said to be less of a problem to hospitals than administration. At least 247 general hospitals were found to have a program in effect, 27 more have equipment ready to use, and numerous others have plans to initiate a program.—*The current status of routine x-raying in general hospitals of the United States, September, 1948, W. H. Oatway, Jr., Arizona Medicine, January, 1949, 6: 23.*—(*W. H. Oatway Jr.*)

A Nonofficial Agency in Britain.—Last December the National Association for the Prevention of Tuberculosis celebrated its fiftieth anniversary. The Association remains a voluntary body, encouraging research and seeking public support. There is a definite place in the National Health Service for the nonofficial agencies which are interested in the prevention of tuberculosis and the next ten years should see no restriction of its activities. Indeed, the prevention of tuberculosis might well form the main task of medical officers of health who are now freed from the routine of hospital administration. At present the Association is extending its activities to the British colonies.—*Tuberculosis and voluntary action, Editorial, Brit. M. J., December 25, 1948, 4599: 1114.*—(*R. W. Clarke*)

BCG Cultures.—The possibility arose that frequent subculturing might alter the biological properties of BCG strains. The problem could easily be solved if the cultures could be kept under standard conditions. A method used successfully with other organisms is to freeze-dry the cultures. The problem was to determine the efficacy of this method with BCG strains. Various vehicles were tried; serum and gelatin proved best. It was found that the survival rate after freeze-drying was about 66 per cent. The cultures were stored for one to twelve months at both 4°C. and 26°C. The survival rate was not affected by the length of storage. Antigenicity was tested by tuberculin tests on immunized guinea pigs and by protection tests against virulent strains. There was no difference in virulence between the frozen-dried cultures and controls.—*Viability of freeze-dried BCG cultures, J. Unger, Tubercle, January, 1949, 30: 2.*—(*A. G. Cohen*)

Respiratory Dead Space.—The volume of the physiological dead space in the respiratory tree was calculated from simultaneous and continuous measurements of the volume flow and nitrogen content of gas expired after the subject changed from breathing air to breathing 99.6 per cent oxygen. In normal subjects the effect of nonuniform measurements of the alveolar gas or dead space can be largely eliminated. The average volume of the physiological dead space in 45 healthy males at rest was 156 cc.; the average expired volume required to wash out the dead space was 325 cc. The physiological dead space was 25.9 per cent of the tidal volume on the average but this value varied widely in different individuals. The volume of the physiological dead space is affected by: (*1*) The anatomical volume of the bronchial tree. Maximal variations in the lung volune during inspiration changed the volume of the dead space by about 100 cc. Voluntary hyperventilation and postexercise hyperpnea increased the volume of the physiological dead space equally, the increase being 100 cc. or less. (*2*) Gas diffusion between terminal bronchioles and alveolar spaces. Prolongation of the inspiratory time by two to three seconds significantly reduced the volume of the physiological dead space and holding the breath for twenty seconds during inspiration caused reduction of 44 to 82 cc. In slow, deep, breathing the increase in the anatomical volume is counteracted by diffusion during the prolonged inspiratory phase. Variations in the rate of the inspiratory volume flow did not affect the volume of the physiological dead space.—*Lung function studies. II. The respiratory dead space, W. S. Fowler, Am. J. Physiol., September, 1948, 154: 405.—(G. C. Leiner)*

Collateral Respiration.—Pulmonary segments are not isolated units and an obstructed segment of a lobe can obtain air from adjacent, ventilated segments. This collateral respiration may amount to as much as 10 per cent of normal exchange, the volune varying directly with the depth of respiration. It may be hindered by phrenicectomy, tight abdominal binders, and inflammation of the contributing segments. The portals for passage of the air, as for liquids and particulate matter, are the "pores of Kohn." Atelectasis may follow interference with collateral respiration. It has been suggested that surgery and other traumata produce histamine-like substances which result in bronchial constriction and hypersecretion, thus setting the stage for the effect of mechanical factors in the development of atelectasis. A series of experiments on dogs has been carried out, using a special occlusive intrabronchial catheter to measure the segmental volumes and oxygen uptake. When histamine is administered intravenously the collateral respiratory function is temporarily abolished. This action can be inhibited by the prior exhibition of antihistaminic dr[illegible] These findings may have application [illegible]he postoperative state.—*Pharmacologic factors influencing collateral respiration: possible relation to the etiology of pulmonary complications, R. D. Alley & G. E. Lindskog, Ann. Surg., September, 1948, 128: 497.—(W. H. Oatway Jr)*

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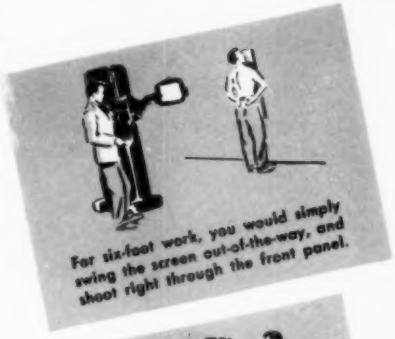

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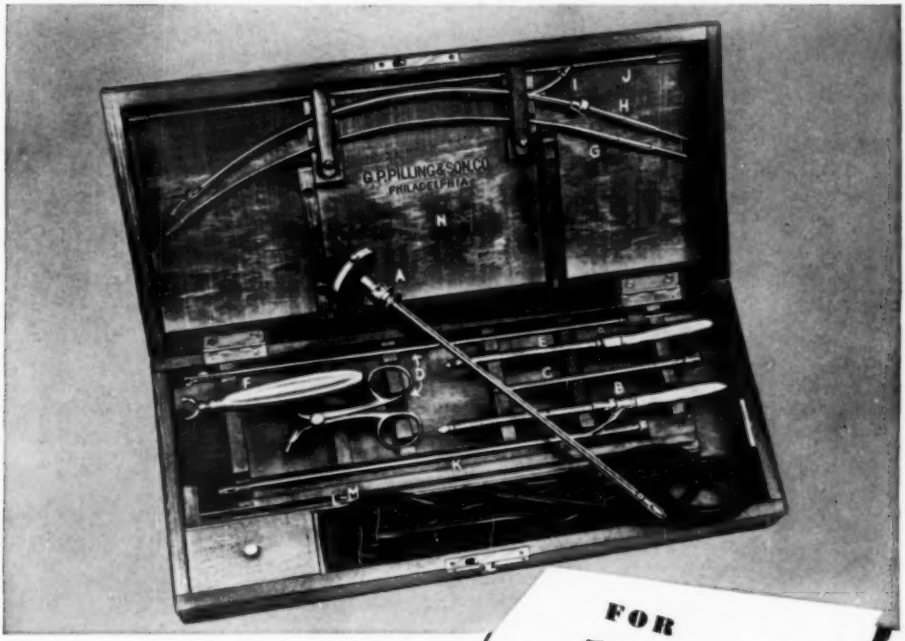

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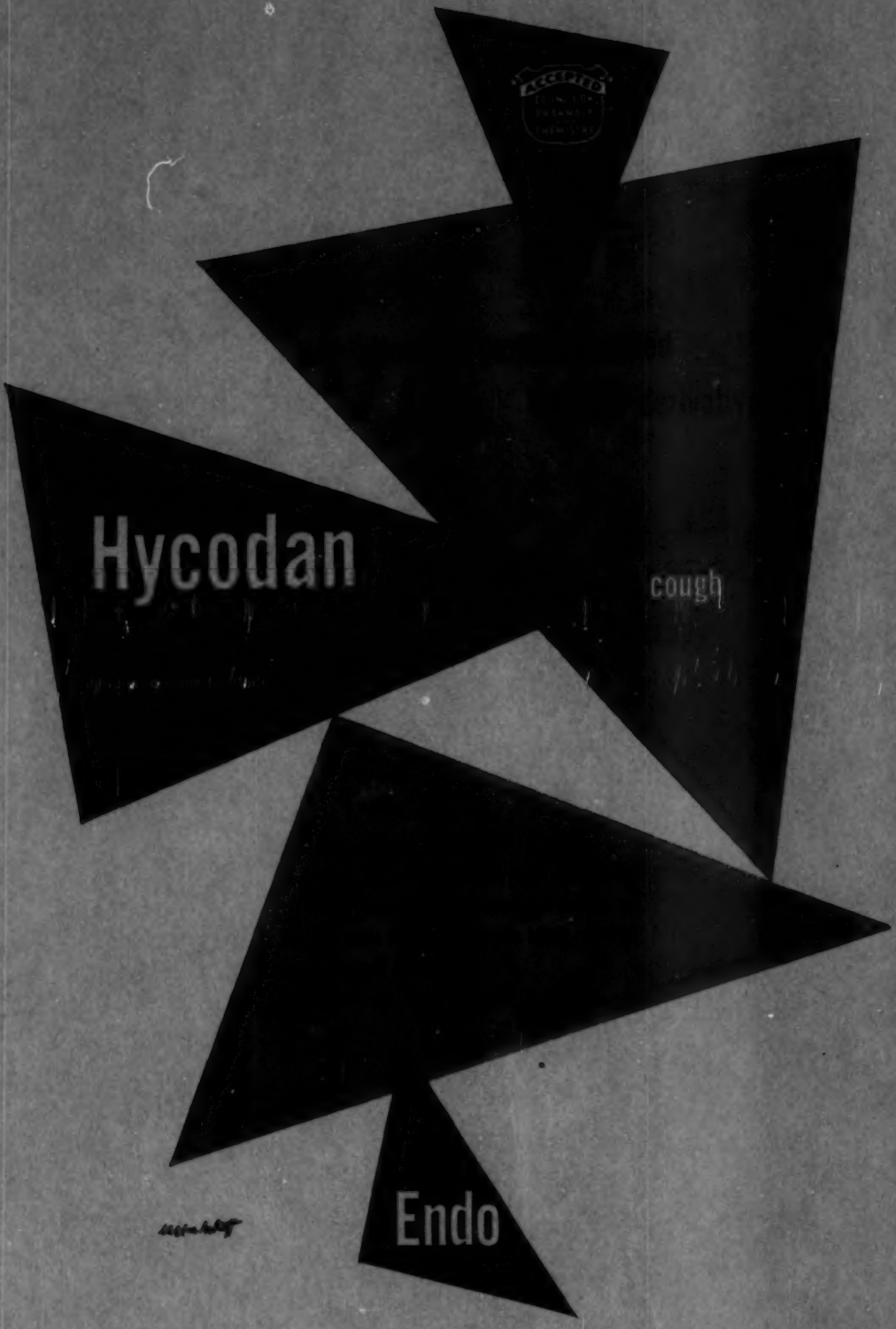
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